Dissertation on

"INCIDENCE OF AUTOIMMUNITY IN TUBERCULOSIS"

Submitted in partial fulfillment for the Degree of

M.D GENERAL MEDICINE

BRANCH – I

THE TAMIL NADU DR.M.G.R MEDICAL UNIVERSITY

CHENNAI

INSTITUE OF INTERNAL MEDICINE

MADRAS MEDICAL COLLEGE

CHENNAI – 600003

CERTIFICATE

This is to certify that the dissertation titled **"INCIDENCE OF AUTOIMMUNITY IN TUBERCULOSIS"** is the bonafide Original work done by **Dr. K. B. SHREEJA**, post graduate student, Institute of Internal medicine, Madras medical college, Chennai-3, in partial Fulfillment of the University Rules and Regulations for the award of MD Branch -1 General Medicine, under our guidance and supervision, during the academic year 2015 - 2018.

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DECLARATION

I, **Dr. K. B. SHREEJA,** solemnly declare that dissertation titled **"INCIDENCE OF AUTOIMMUNITY IN TUBERCULOSIS"** is a bonafide work done by me at Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai-3 during 2017 under the guidance and supervision of my unit chief **Prof.Dr.G.Sundaramurthy, M.D.,** Professor of Medicine, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai.

This dissertation is submitted to Tamilnadu Dr. M.G.R Medical University, towards partial fulfillment of requirement for the award of **M.D.DEGREE IN GENERAL MEDICINE BRANCH-I**.

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Above all I thank my God Almighty for His immense blessings and guidance.

ABBREVIATIONS

APC	:	Antigen Presenting Cell
AFB	:	Acid Fast Bacilli
ANA	:	Anti nuclear Antibody
ANCA	:	Anti-neutrophil Cytoplasmic Antibody
BCR	:	B cell Receptor
CBNAAT	:	Cartridge Based Nucleic Acid Amplication Technique
CMI	:	Cell Mediated Immunity
CD	:	Cluster of Differentiation
CTD	:	Connective Tissue Disorders
CBC	:	Complete Blood Count
DM	:	Diabetes Mellitus
ELISA	:	Enzyme Linked Immunosorbent Assay
EPTB	:	Extrapulmonary TB
HBsAg	:	Hepatitis B surface antigen
HCV	:	Hepatitis C virus

HLA	:	Human Leucocyte Antigen
HIV	:	Human Immunodeficiency Virus
HSP	:	Heat Shock Protein
INH	:	Isoniazid
INF	:	Interferon
IGRA	:	Interferon gamma Release Assay
LPA	:	Line Probe Assay
OIF	:	Oil Immersion Field
PTB	:	pulmonary tuberculosis
PLHIV	:	Person living with HIV
RF	:	Rheumatoid factor
Rif	:	Rifampicin
SLE	:	Systemic Lupus Erythematosis
TCR	:	T cell Receptor
TNF	:	Tumour Necrosis Factor

CONTENTS

INTRODUCTION

INTRODUCTION

Autoimmune diseases are a leading cause of morbidity and mortality. The autoimmune disease results from inappropriate response of immune system to self antigens. Etiology of autoimmune disease remains largely unknown but candidate etiological factors include genetic abnormalities and infections. The role of infections in triggering autoimmunity is possibly due to two mechanisms:

1. Up regulation of co stimulators on Antigen presenting cells which present the self antigen to T cells resulting in breakdown of clonal anergy.
2. Molecular mimicry – Microbes may express antigens that have the same amino acid sequence as self antigens.

Tuberculosis is known to be associated with many auto immune disorders. Populations with exposure to tuberculosis have higher incidence of autoimmune disorders whereas population without any exposure have low incidence.

Patients attending Thoracic Medicine and Internal Medicine OPD or admitted in the wards were subjected to detailed history taking, clinical examination and blood investigations like CBC, Renal function tests, Liver function tests, HIV, HBsAg and Anti-HCV. Chest X ray, Sputum / tissue/ fluid AFB, Sputum / tissue/ fluid gene expert analysis was done depending on the diagnosis.

Immunological testing for ANA (Antinuclear Antibody) by ELISA method was done for all the patients. Those who were found to be ANA positive underwent ANA profiling for detecting specific autoantibody.

AIMS AND OBJECTIVES

AIMS AND OBJECTIVES

To study the incidence of autoimmunity in Pulmonary and extrapulmonary Tuberculosis.

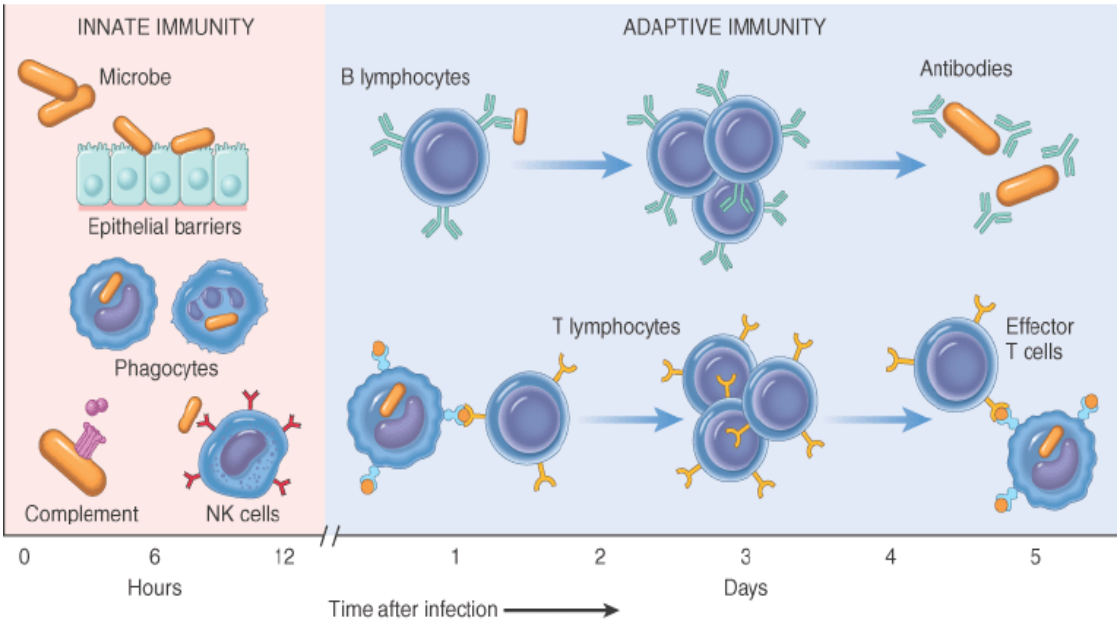
REVIEW OF LITERATURE

REVIEW OF LITERATURE

The human body defends itself from infectious agents and other foreign substances in its environment by many layers of defense which includes physical barriers like skin, protective chemical substances in blood and tissue fluids and physiological reaction of tissue to injury or infection. Whenever a pathogen with the potential to cause tissue injury or disease breaches the surface barriers and enters the body, it encounters inner defense mechanisms that have been grouped into 2 more/less distinct functional systems called innate / natural immunity and acquired immunity.

Types of immunity - Innate immunity is the inborn resistance that is already present the first time a pathogen is encountered. It does not require prior exposure and is not modified significantly by repeated exposures to the pathogen. Acquired immunity is the resistance that is weak/absent on first exposure but increases with subsequent exposure to the same specific pathogen. Both immune systems are made up of numerous components – specialized cells that recognize , sequestrates and eliminates various types of organisms/ harmful substances collectively known as cell mediated immunity (CMI) ; Soluble macromolecules (usually proteins) that circulate in blood and extracellular fluids making these inhospitable to foreign invaders known as humoral immunity. Both systems usually act in concert

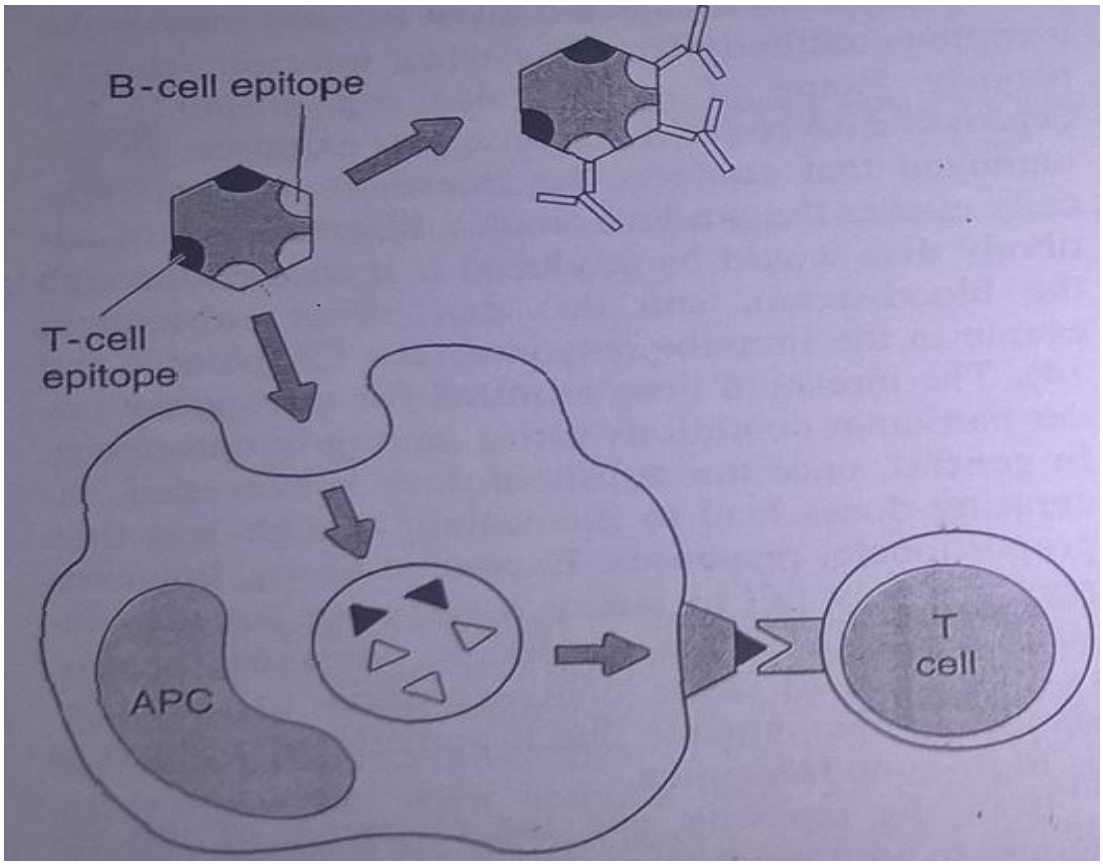
and often depend on each other to produce their maximal effect. The action of one system influences the other.



Innate immunity mainly recognizes substances like distinctive carbohydrates, lipids and N-formylated peptides that are foreign per se. Acquired immune responses are most commonly directed against proteins – a class of molecules found in both the pathogens and in host. Discrimination between self and nonself is absolutely essential so that it normally coexists peacefully with all of the organic materials that make up the post but response vigorously against foreign organisms and cells from other people with extreme specificity.

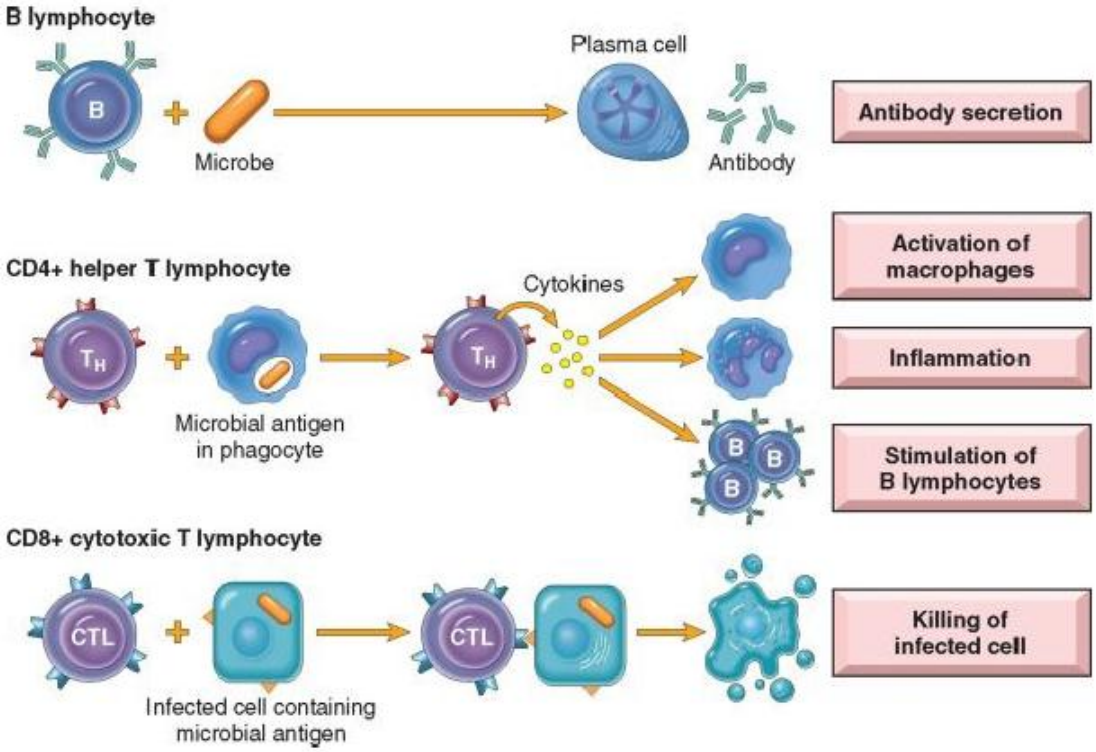
An Immunogen is any substance capable of inducing an immune response. Immune responses are carried out only by those B & T cell clones whose surface immunoglobulin or T cell receptor (TCR) proteins

recognize the Immunogen. Substances that are recognized by a particular immunoglobulin or TCR and hence can serve as target of immune response are called antigens. An epitope is the specific site to which a particular immunoglobulin or TCR binds. The immune system normally discriminates between self and non self so that only molecules that are foreign to the host are immunogenic.

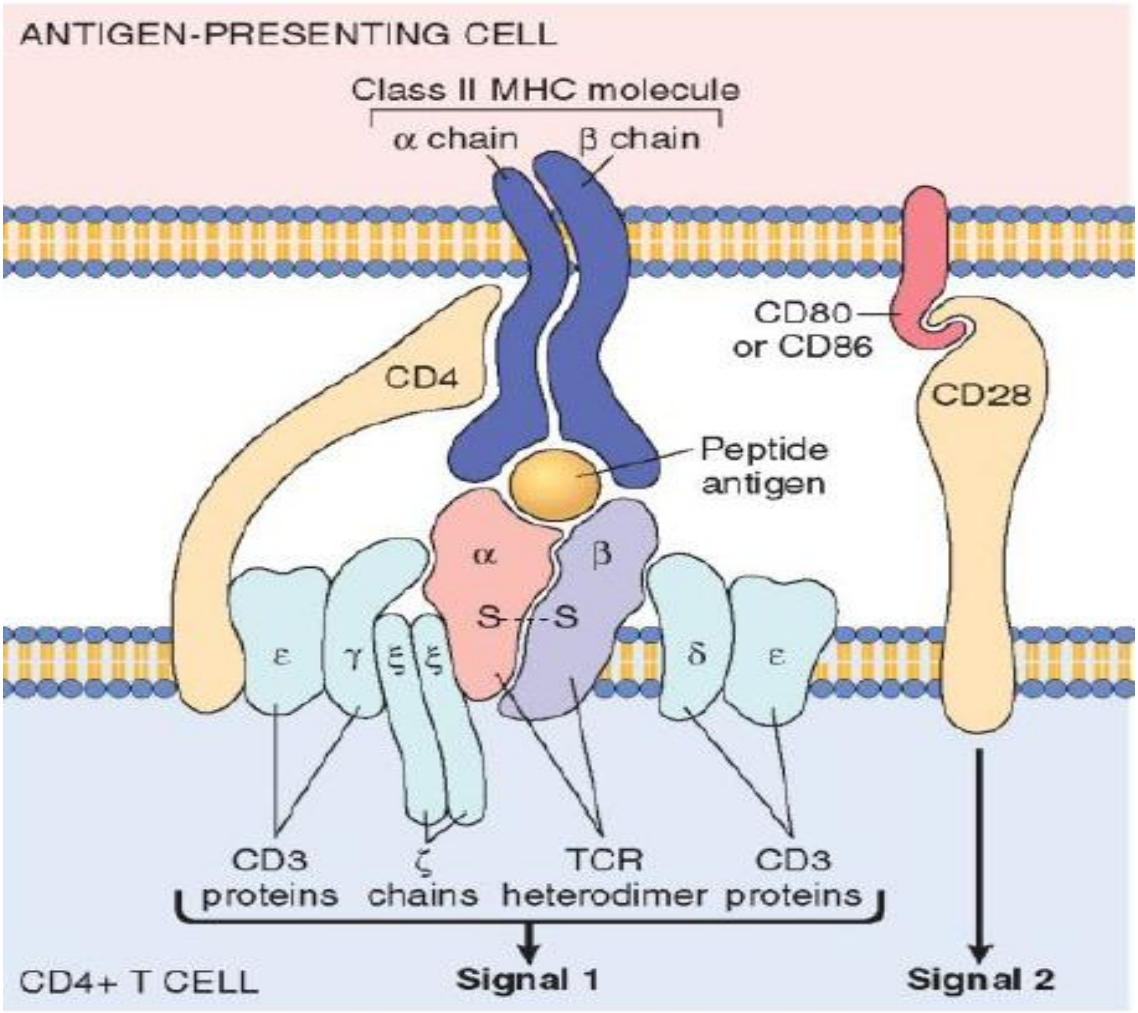


The TCR only recognizes the complexes formed by peptides bound to Major Histocompatibility Complex (MHC) proteins on surface of host cells. It involves antigen processing (cleaving proteins into peptides) and antigen presentation.

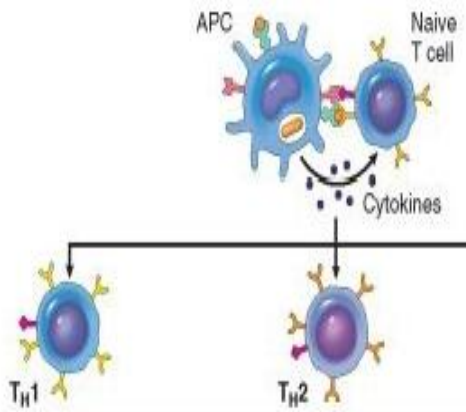
Function of B and T lymphocytes:



T cell activation by antigen:

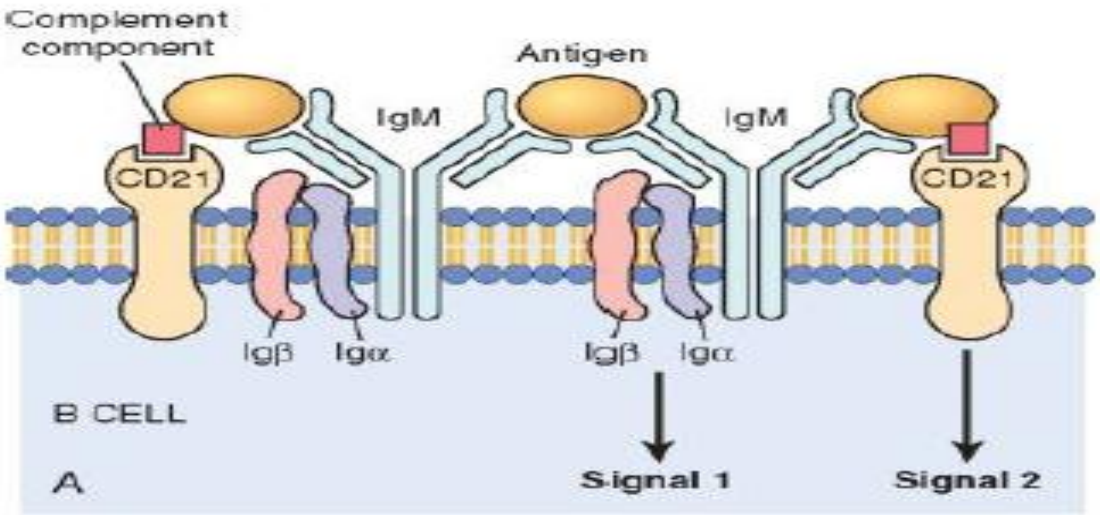


Subsets of T helper cells:

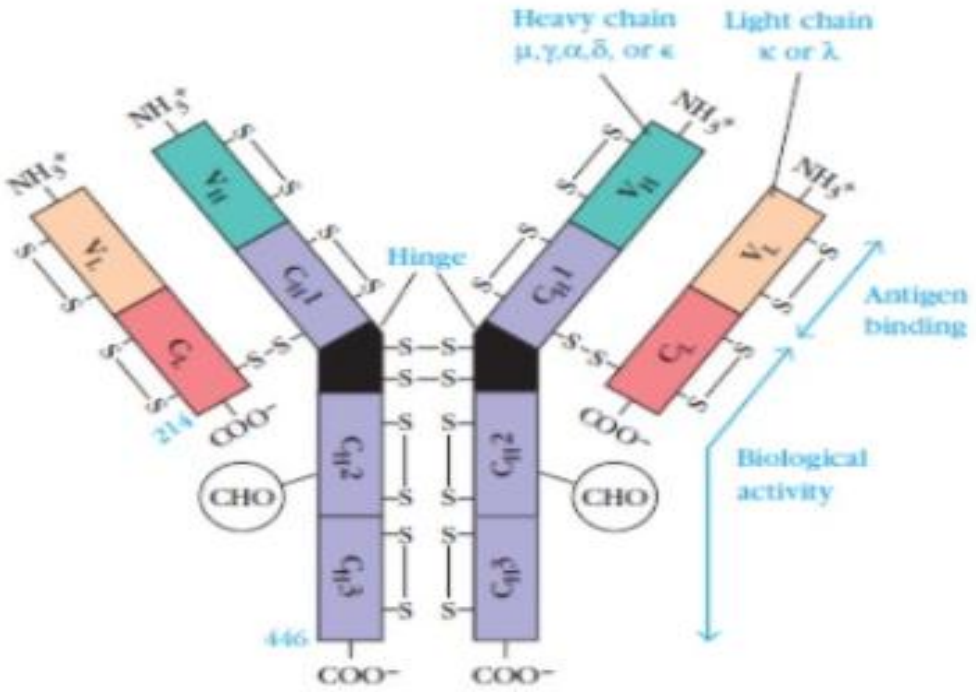


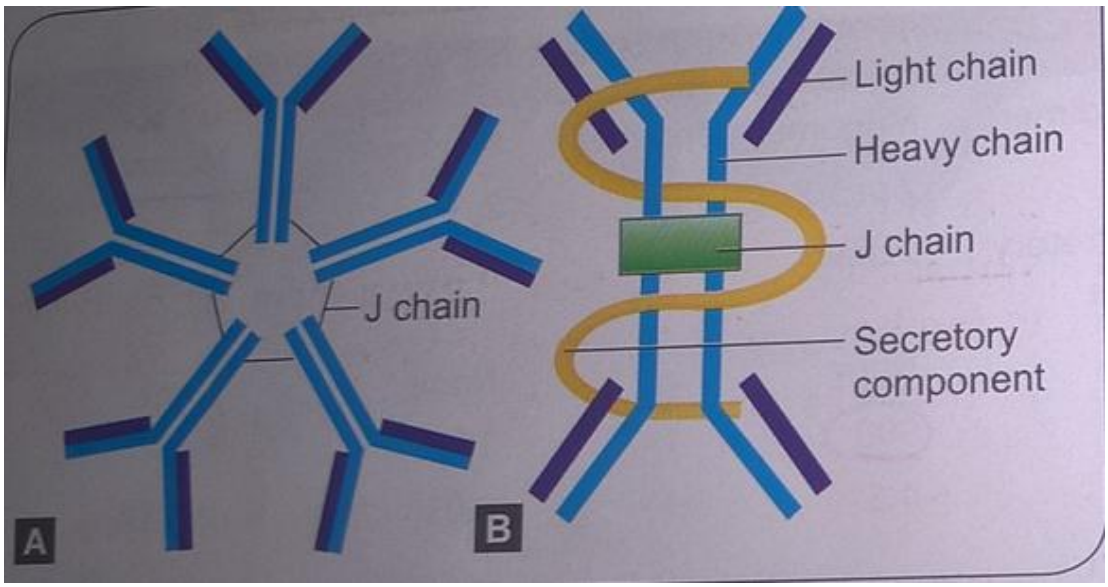
Cytokines produced	IFN-γ	IL-4, IL-5, IL-13	IL-17, IL-22, chemokines
Cytokines that induce this subset	IFN-γ, IL-12	IL-4	TGF-β, IL-6, IL-1, IL-23
Immunological reactions triggered	Macrophage activation, stimulation of IgG antibody production	Stimulation of IgE production, activation of mast cells and eosinophils	Recruitment of neutrophils, monocytes
Host defense against	Intracellular microbes	Helminthic parasites	Extracellular bacteria, fungi
Role in disease	Immune-mediated chronic inflammatory diseases (often autoimmune)	Allergies	Immune-mediated chronic inflammatory diseases (often autoimmune)

B cell activation by antigen:

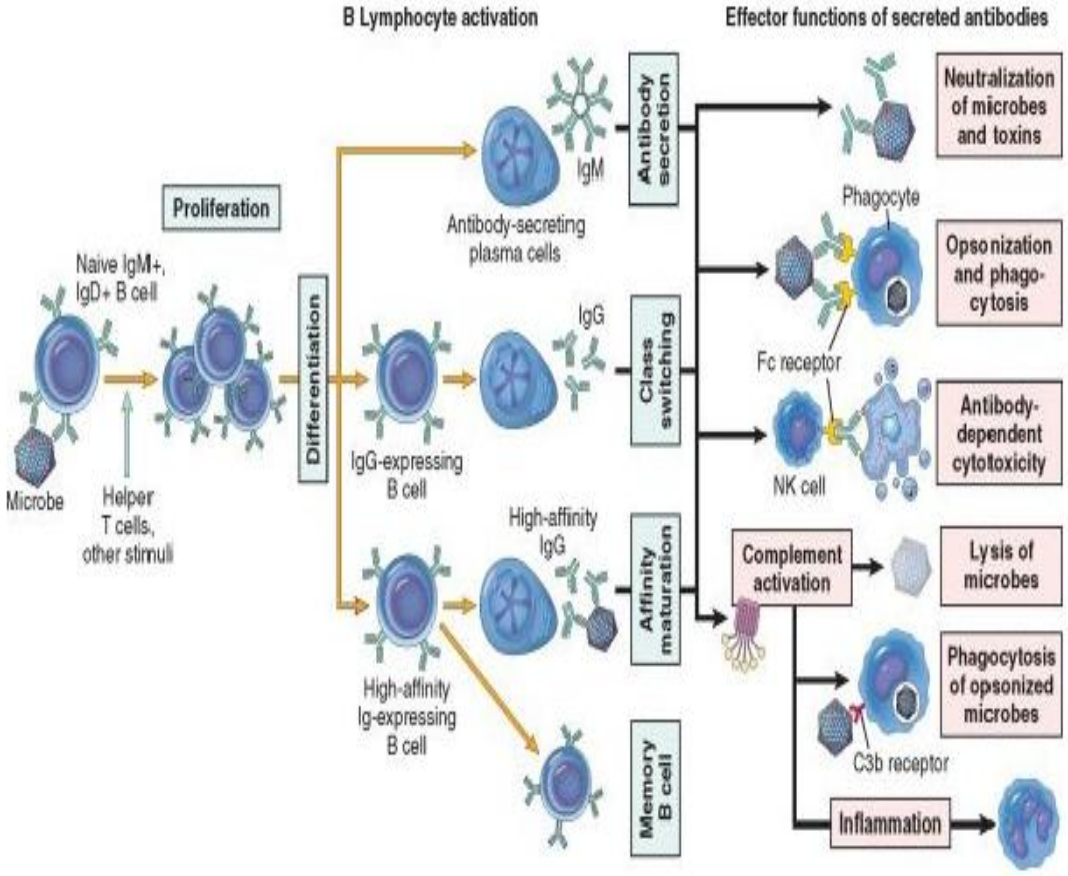


Structure of Immunoglobulin:





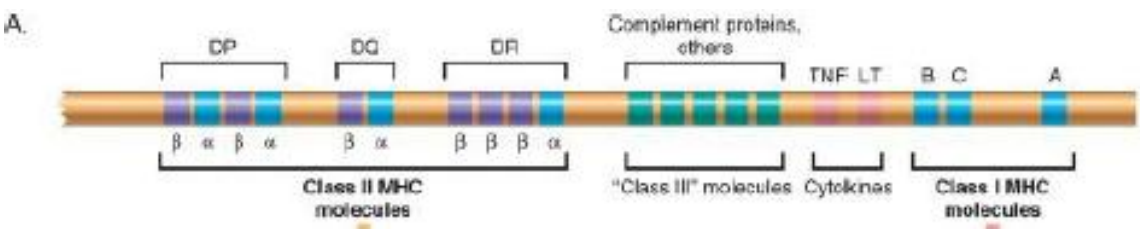
Role of B lymphocytes:



Major histocompatibility complex (MHC) –

The function of MHC molecules is to display peptide fragments of proteins for recognition by antigen-specific T cells. The genes encoding the major histocompatibility molecules are present on chromosome 6, the major histocompatibility complex, or the human leukocyte antigen (HLA) complex, named because in humans MHC-encoded proteins were initially detected on leukocytes by the binding of antibodies. The HLA system is highly polymorphic. There are many alleles of each MHC gene in the population and each individual inherits one set of these alleles that is different from the alleles in most other individuals. The MHC genes have evolved by sequential duplications so that each person inherits multiple class I and class II genes. There are three separate genes designated HLA-A, HLA-B and HLA-C that each codes for MHC class I alpha chains. HLA- DP, PQ, DR codes for MHC class II gene loci.

Location of genes in HLA complex:



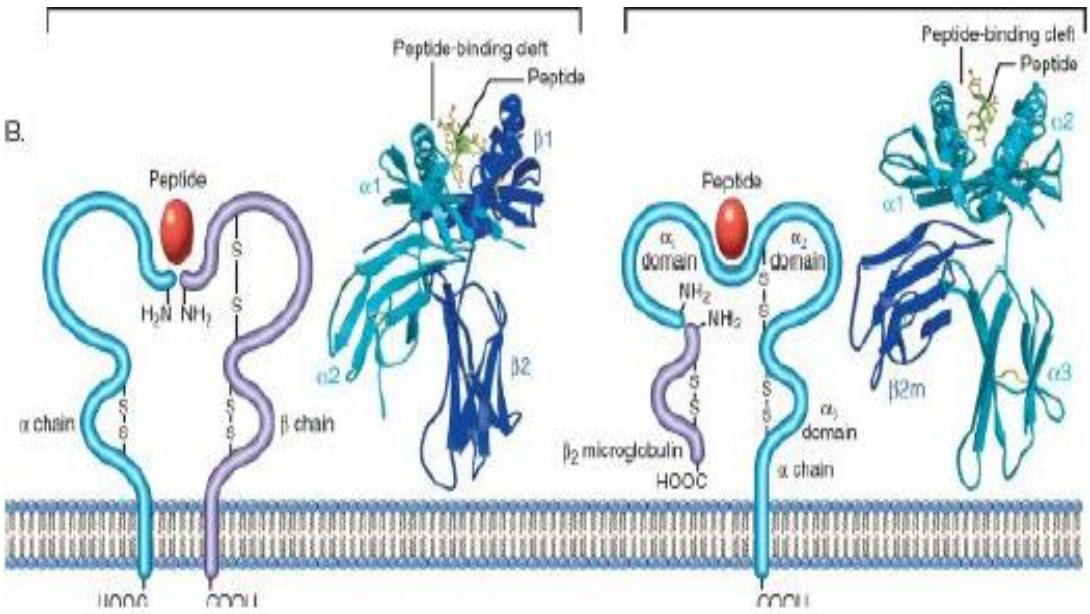
MHC class I molecule:

Class I MHC molecules are expressed on all nucleated cells and platelets. They are encoded by three closely linked loci, designated HLA-A, HLA-B, and HLA-C.

MHC class II molecule:

Class II MHC molecules are expressed on APC and are encoded in a region called HLA-D, which has three sub regions: HLA-DP, HLA-DQ, and HLA-DR.

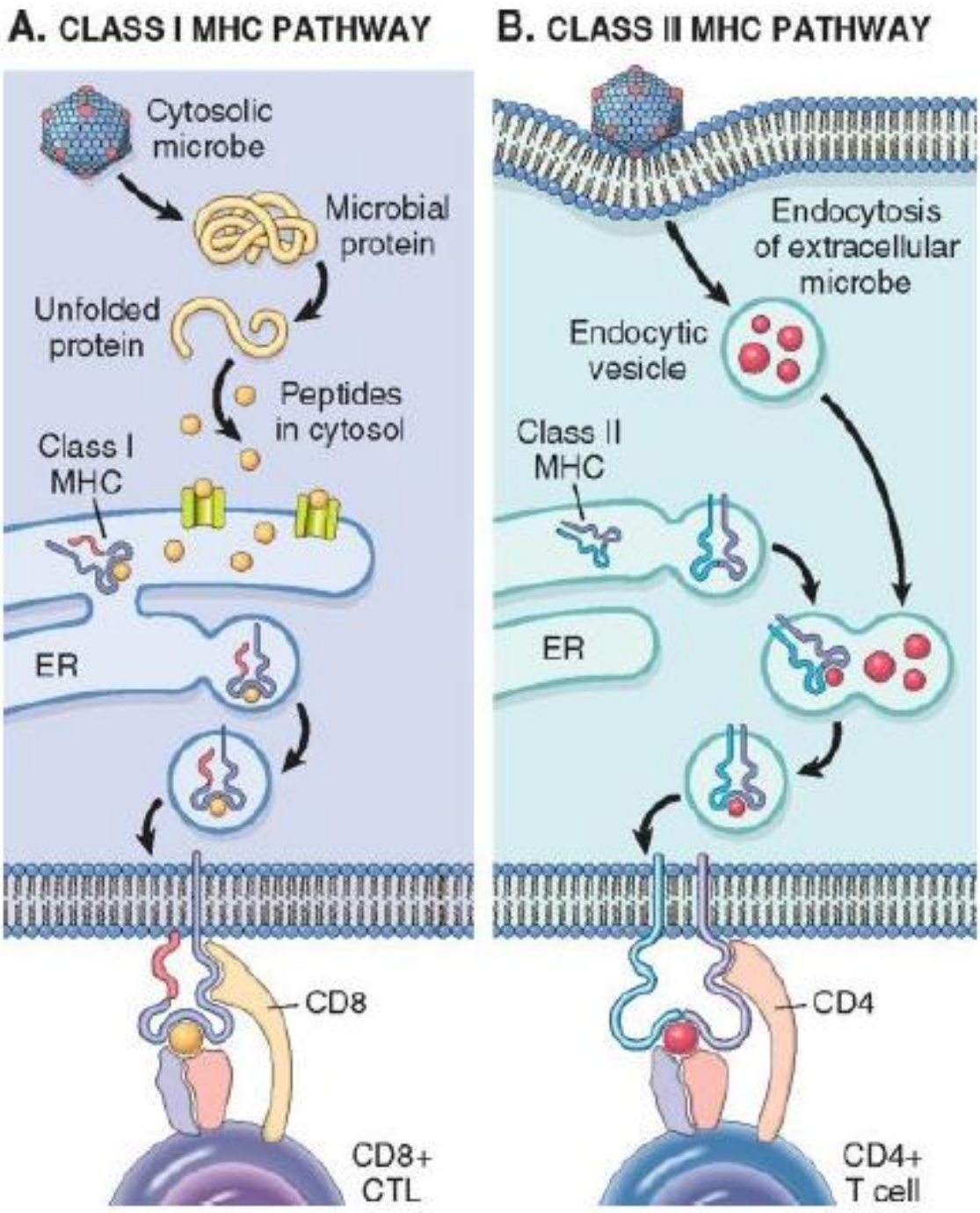
Structure of MHC class I and class II molecules:



Antigen processing and presentation by MHC molecules:

- In the class I MHC pathway, peptides produced from proteins in the cytoplasm and are transported to the endoplasmic reticulum (ER), where they bind to class I MHC molecules. The peptide-MHC complexes are transported to the cell surface and displayed for recognition by CD8+ T cells. E.g. Immune response against viruses and Tumour cells.

- In the class II MHC pathway, proteins are ingested into vesicles and degraded into peptides, which bind to class II MHC molecules being transported in the same vesicles. The class II–peptide complexes are expressed on the cell surface and recognized by CD4+ T cells. E.g. Immune response against extracellular microbes and soluble proteins.


A. CLASS I MHC PATHWAY
B. CLASS II MHC PATHWAY
Cytosolic microbe
Microbial protein
Unfolded protein
Peptides in cytosol
Class I MHC
ER
CD8
CD8+ CTL
Endocytosis of extracellular microbe
Endocytic vesicle
Class II MHC
ER
CD4
CD4+ T cell

HLA association with autoimmune disease:

Disease	HLA allele	Relative risk
Class II associated		
Hashimoto's disease	*DR5*	3.2
Graves' disease	*DR3*	3.7
Type 1 diabetes	*DQ8* *DQ2 + DQ8* *DQ6*	14 20 0.2
Addison's disease	*DR3*	6.3
Rheumatoid arthritis	*DR4*	5.8
Sjögren's syndrome	*DR3*	9.7
Multiple sclerosis	*DR2*	3
Class I associated		
Ankylosing spondylitis	*B27*	87.4
Myasthenia gravis	*B8*	3

Autoimmune diseases:

Autoimmune disorders are thought to involve an inappropriate immune attack against self tissues. The mere presence of autoantibodies does not indicate an autoimmune disorder exists. Autoantibodies can be found in the serum of apparently normal individuals especially older age groups and chronic infections. Innocuous autoantibodies are sometimes produced after damage to tissues and may serve a physiological role in removal of tissue breakdown products.

Ideally at least three requirements should be met before a disorder is categorized as truly autoimmune in nature.

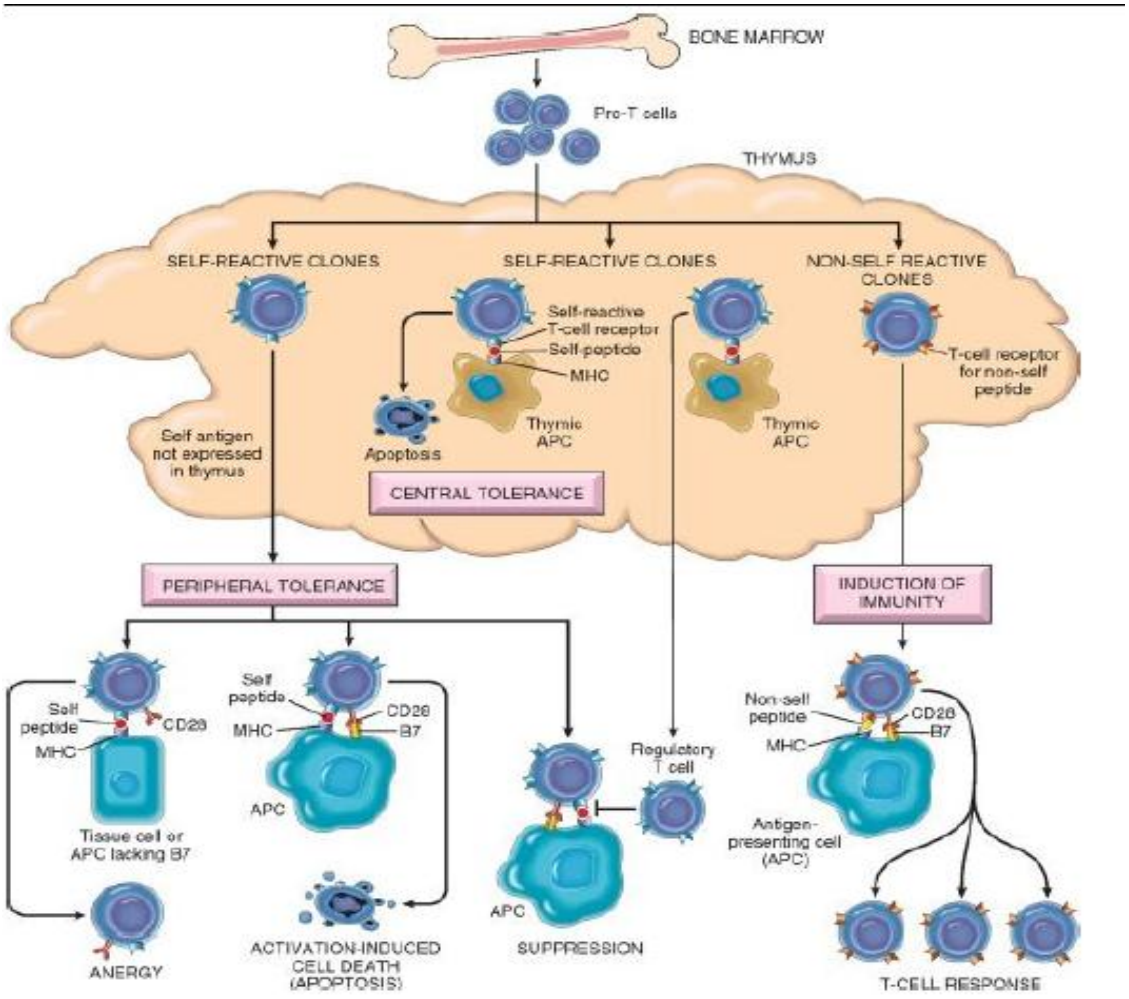
- Presence of immune reaction specific for some self antigen or self tissue.
- Evidence that such a reaction is not secondary to tissue damage but is of primary pathogenic significance.
- Absence of another well-defined cause of disease

Immunological tolerance:

Immunological tolerance is the phenomenon of unresponsiveness to antigens induced by exposure to lymphocytes to that antigen. Self-tolerance refers to lack of responsiveness to an individual's own antigens. Self-tolerance includes central and peripheral tolerance.

Type	Cell Type	Site	Mechanism
Central Compartment			
Central tolerance	T cells	Thymus	Primarily deletion, anergy, possibly editing
	B cells	Bone marrow	Editing, anergy, deletion
Peripheral Compartment			
Immature B cell tolerance	Transitional 1 (T1) B cells	Periphery	Deletion, anergy upon activation
Peripheral anergy	T and B cells	Secondary lymphoid organs and peripheral tissue	Inadequate signal induces cell inactivation
Ignorance	T cells; maybe B cells	Peripheral and secondary lymphoid organs	Insufficient self-antigen or co-stimulation
Inaccessible self-antigen	T and B cells	Peripheral organs	Sequestration, crypticity
Regulation	T and B cells	Secondary lymphoid organs and site of inflammation	Suppression by regulatory cells via intercellular signals and cytokines
Clonal deletion following activation	T and B cells	Site of inflammation and secondary lymphoid organs	Apoptosis caused by a decline in survival factors
Cytokine deviation	T cells	Site of inflammation and secondary lymphoid organs	Differentiation toward less pathogenic Th subsets
Postsomatic hypermutation	B cells	Germinal center	Insufficient CD4 T cell help, deletion (via *Fas*)
Tissue resistance	B and T cells	Peripheral tissues	Inhibitory intercellular signals and cytokines
Innate Mechanisms			
PRR engagement required for activation	Innate cells	Site of inflammation	Simple mechanism for self-nonself discrimination
Suppression of adaptive immune responses	Immature and mature DCs	Site of inflammation and secondary lymphoid organs	Delivery of inhibitory signals and activation of Treg
Clearance of apoptotic cells	Complement, phagocytes	Peripheral tissues	Removal of potential proinflammatory material and self-antigens
Complement-mediated	Lymphocytes, innate cells	Secondary lymphoid organs	Modulation of activation

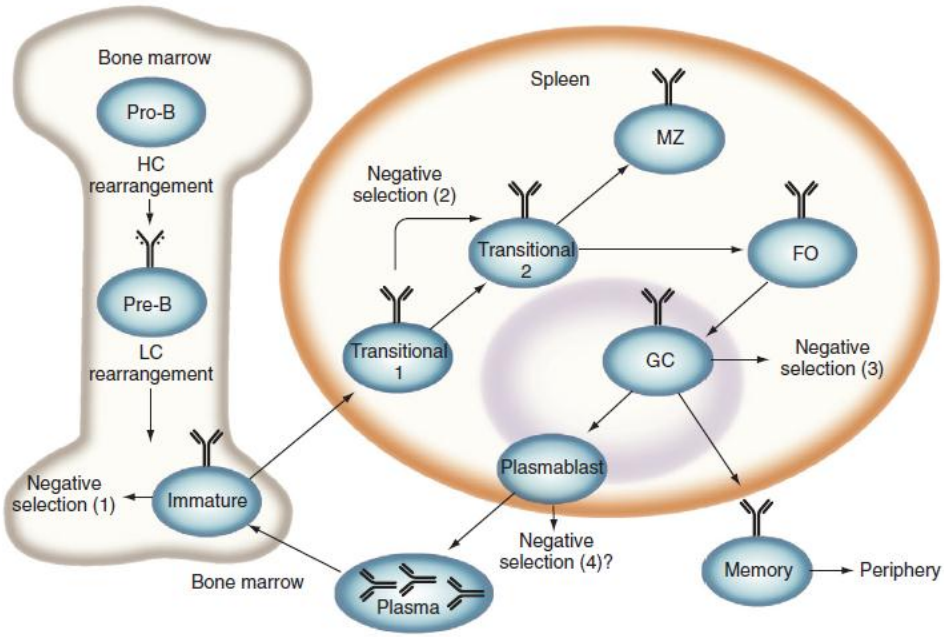
MECHANISMS OF CENTRAL AND PERIPHERAL TOLERANCE TO SELF ANTIGENS:



Peripheral tolerance:

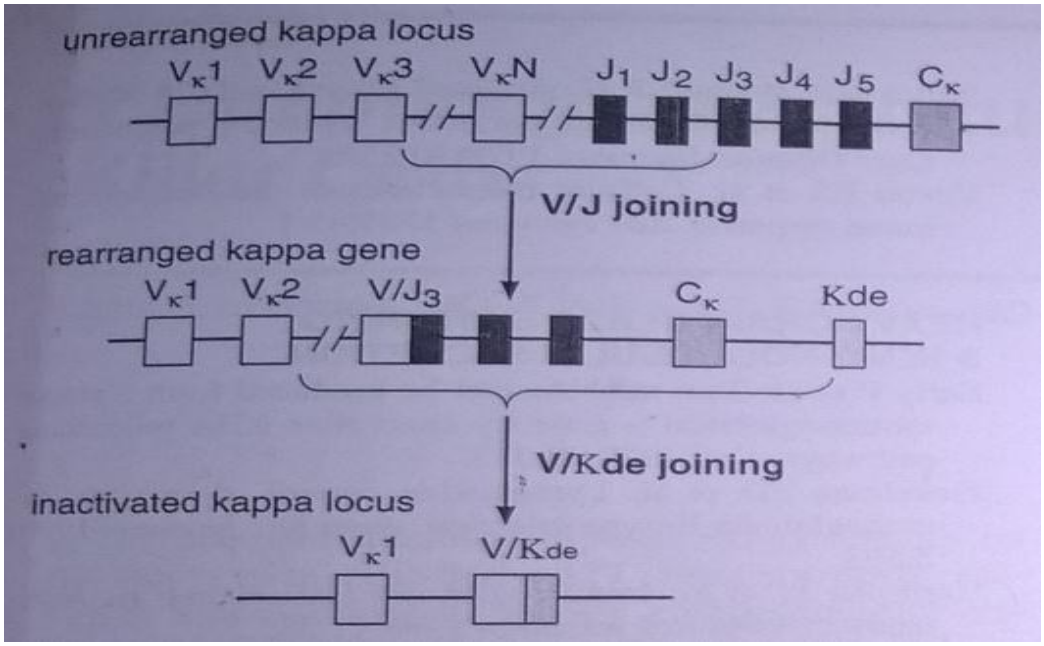
- Anergy
- Suppression by regulatory T cells
- Deletion by apoptosis – occurs by two mechanisms: Fas- Fas ligand system, T cells that recognize self-antigens may express proapoptotic member of Bcl family (Bim) without antiapoptotic members of the family like Bcl-2 and Bcl-x thereby triggering apoptosis by mitochondrial pathway.
- Sequestered antigens – Tissues in which these antigens are located do not communicate with blood and lymph like testis, eye and brain.

Selection check points in B cell maturation:



- Clonal deletion: When a mature B cell contacts an antigen in the absence of appropriate T cell help, the B cell either dies or loses its ability to carry out an immune response depending on the antigen. In case of membrane bound or particulate antigen, the self-reactive B cell generally dies.
- Clonal anergy: Soluble protein antigens which generate weaker signals through BCR of self-reactive B cells make the cell unresponsive to activating stimuli.
- The random assembly of V, D, and J segments during lymphopoeisis inevitably produces some B cell clones whose Immunoglobulin recognize self antigenic determinants on normal host cells or tissues. Auto reactive immunoglobulin are deleterious to host and are not secreted. B cells that make auto reactive Immunoglobulin are silenced in two ways:
    - Immature B cells that contact antigens in bone marrow shortly after it begins expressing surface Immunoglobulin results in maturational arrest. The cell fails to mature further and does not exit the marrow.
    - Receptor editing occurs, whereby a self reactive immature B cell attempts to change its light chain and thereby its antigen specificity.

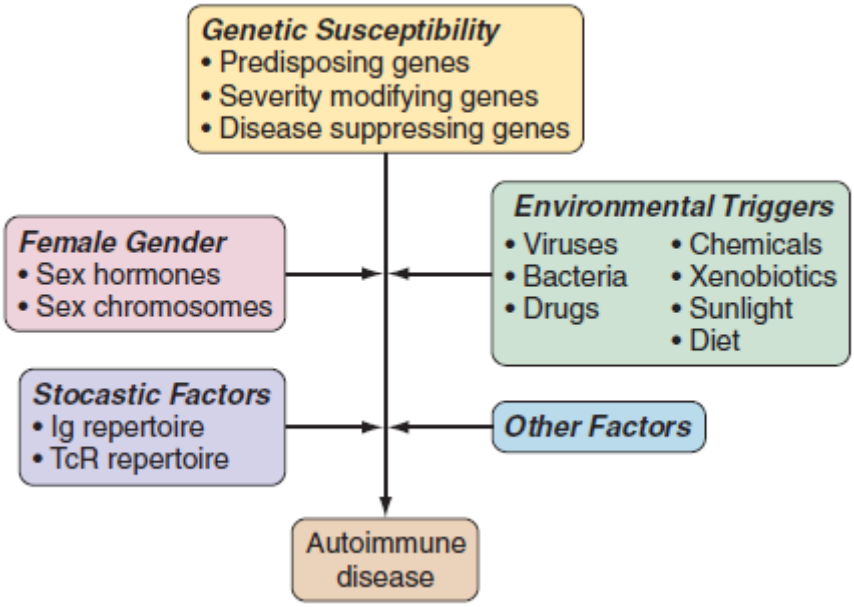
- If receptor editing fails, then the auto reactive B cells remains arrested in undifferentiated state and eventually dies. This mechanism is effective for self antigens found in bone marrow and ubiquitous cell surface or extracellular matrix proteins.



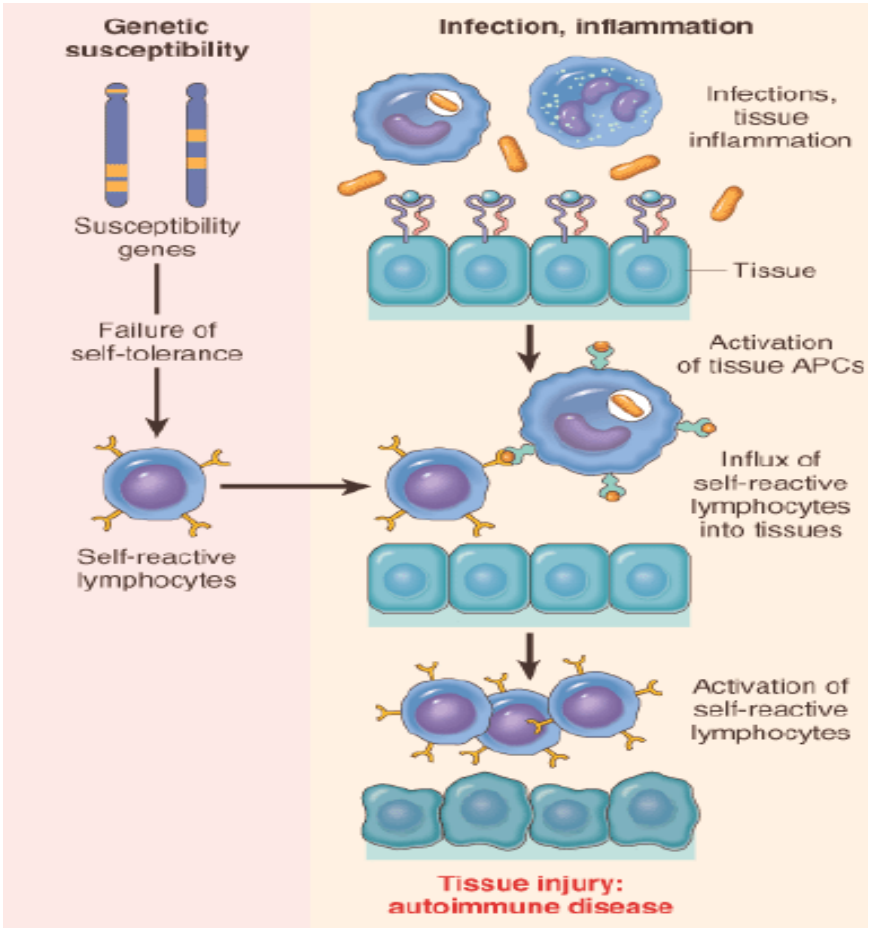
Criteria for autoimmune diseases:

Indications that a disease is autoimmune
Presence of high titer autoantibodies and/or autoreactive lymphocytes *in vivo*
Autoantibody binding and/or T-cell reactivity to autoantigen *in vitro*
Transfer of disease with autoreactive serum and/or autoreactive lymphocytes
Immunopathology consistent with autoimmune-mediated processes
Beneficial effect of immunosuppressive interventions
Exclusion of other possible causes of disease
MHC association
Animal model mirroring the human disease

Etiology of autoimmune diseases:



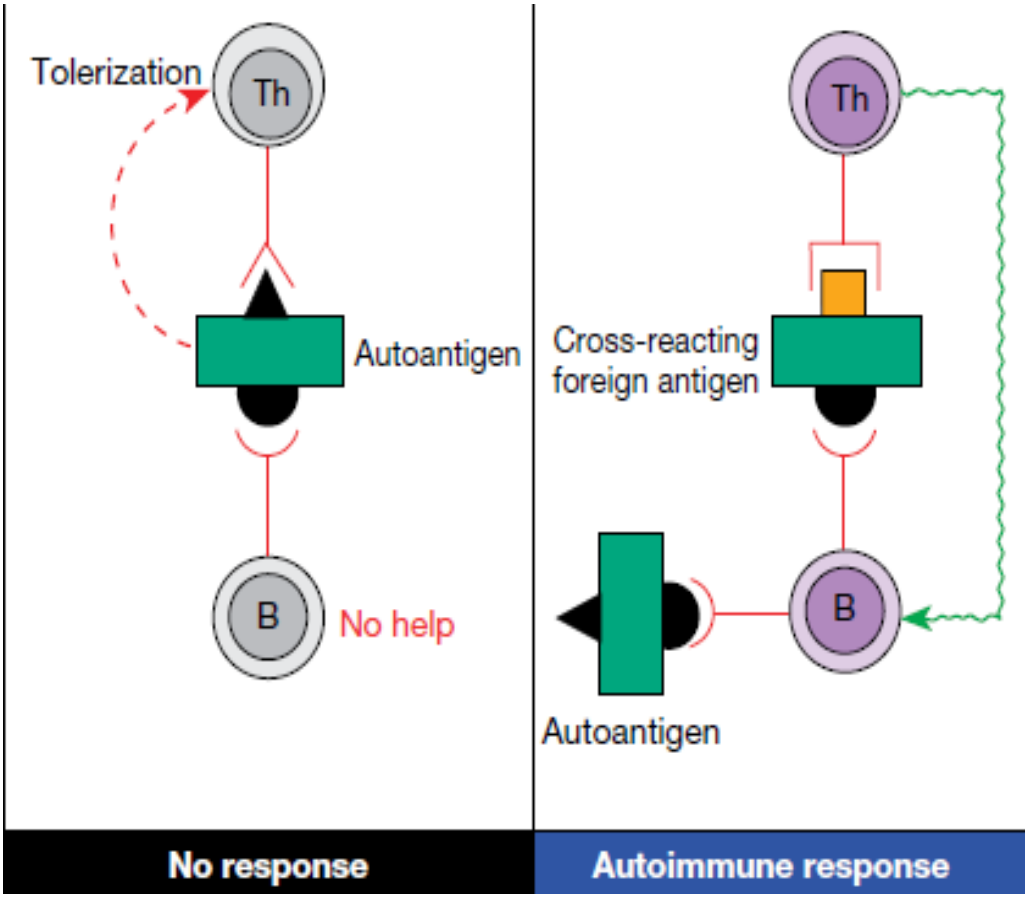
Pathogenesis of autoimmunity:



Mechanisms in autoimmune disease:

- Loss of tolerance
- Visibility of sequestered antigens to immune system
- Obtaining T cell help for auto antigen specific B cells :

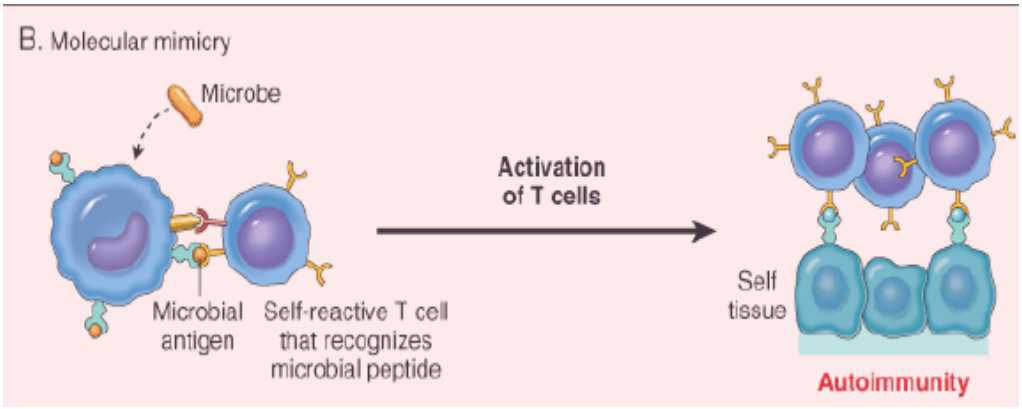
  The absence of functional self-reactive helper T-cells can be circumvented by microbial cross-reactive antigens that share some, but not all, epitopes with self antigens



- Modification of auto antigen :

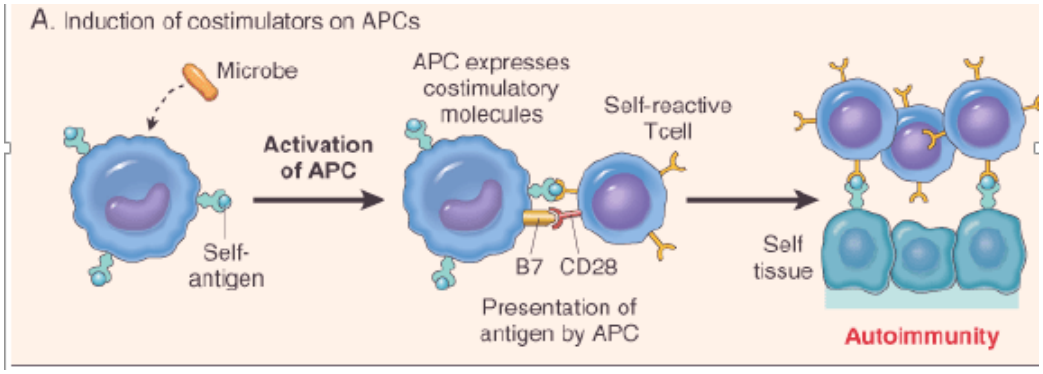
  E.g.: citrullination of vimentin, fibrinogen, collagen type II, and α-enolase in RA; combination with a drug like alpha methyl dopa

- Molecular mimicry of T cell epitope :

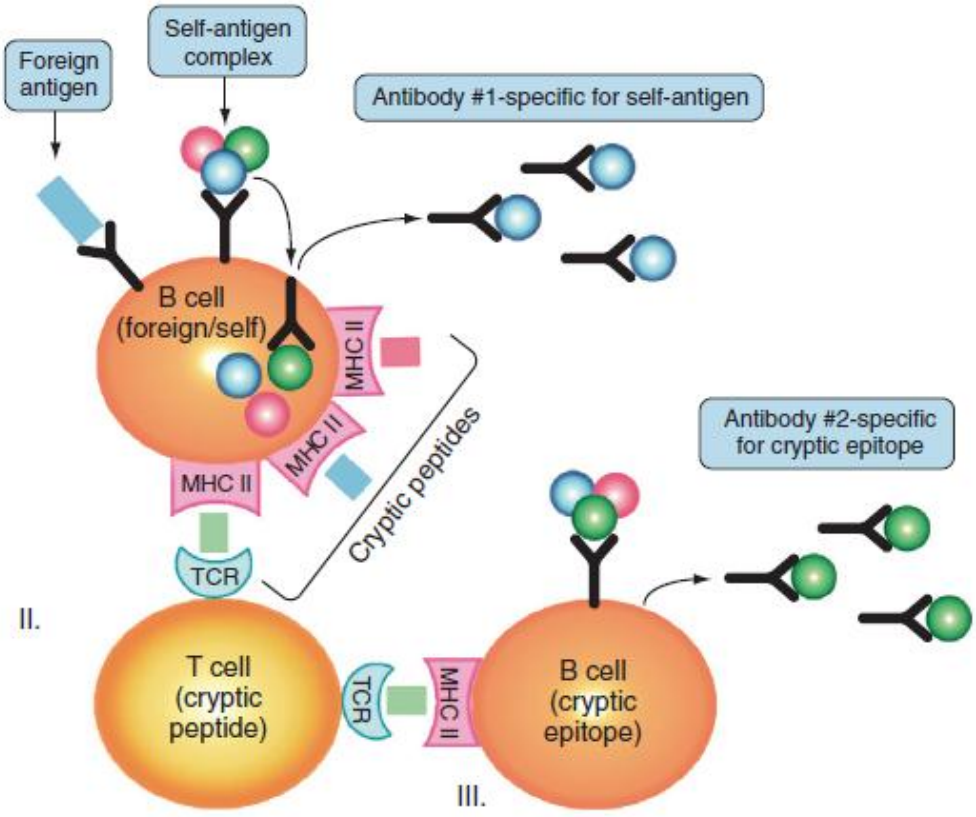


Disease	Microbial molecule		Sequence
Rheumatoid arthritis	Microbe:	*Escherichia coli*	QKRAAVDTY
	Self:	HLA-DRB1*04:01	QKRAAYDQY
Multiple sclerosis	Microbe:	Epstein–Barr virus	VYHFVKKHV
	Self:	Myelin basic protein	VVHFFKNIV
Multiple sclerosis	Microbe:	*Chlamydia pneumoniae*	YGCLLPRNPRTEDQN
	Self:	Myelin basic protein	YGSLPQKSQRTQDEN
Type 1 diabetes	Microbe:	Hepatitis C virus	AAARRWAC
	Self:	Glutamic acid decarboxylase 65	AAARKAAC
Myasthenia gravis	Microbe:	Polio virus	TKESRGTT
	Self:	Acetylcholine receptor	IKESRGTK
Rheumatic fever	Microbe:	*Streptococcus pyogenes*	LTDQNKNLTTEN
	Self:	Cardiac myosin	LTSQRAKLQTEN

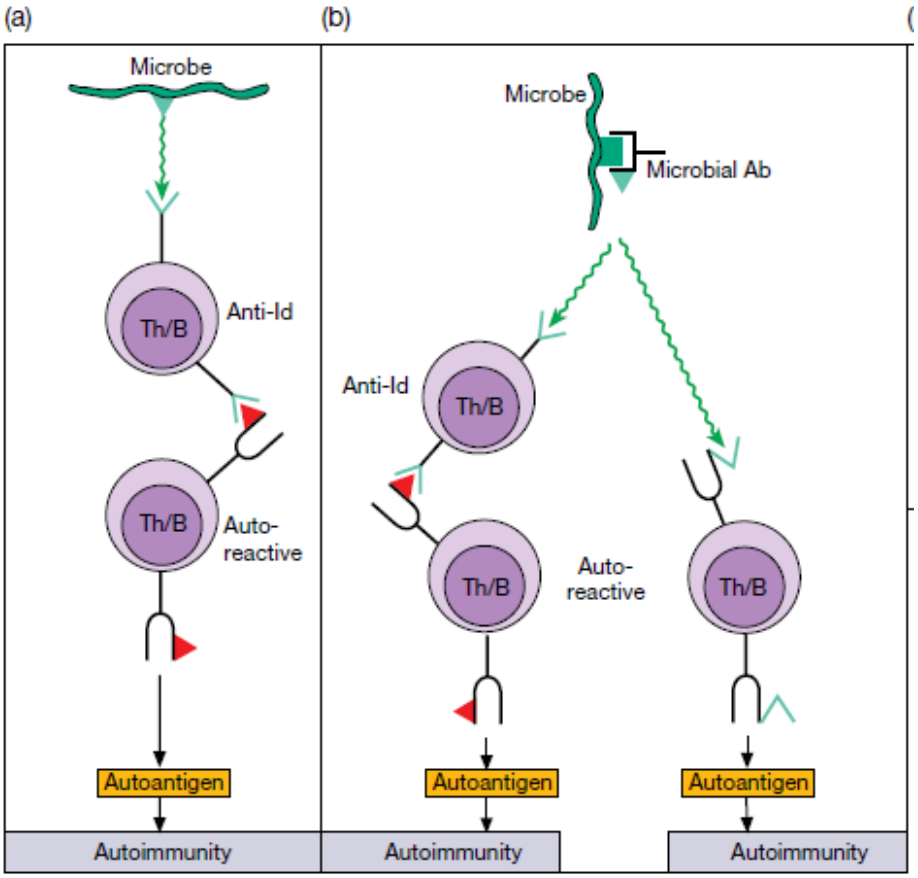
- Induction of co stimulators on APC :



- Piggy-back" T-cell epitopes and epitope spread :



- Idiotype bypass mechanisms :



- Polyclonal activation :

  Bacterial endotoxin

- Regulatory defects

- Aberrant expression of MHC class II

- Cytokine imbalance

Autoantibodies in systemic autoimmune diseases:

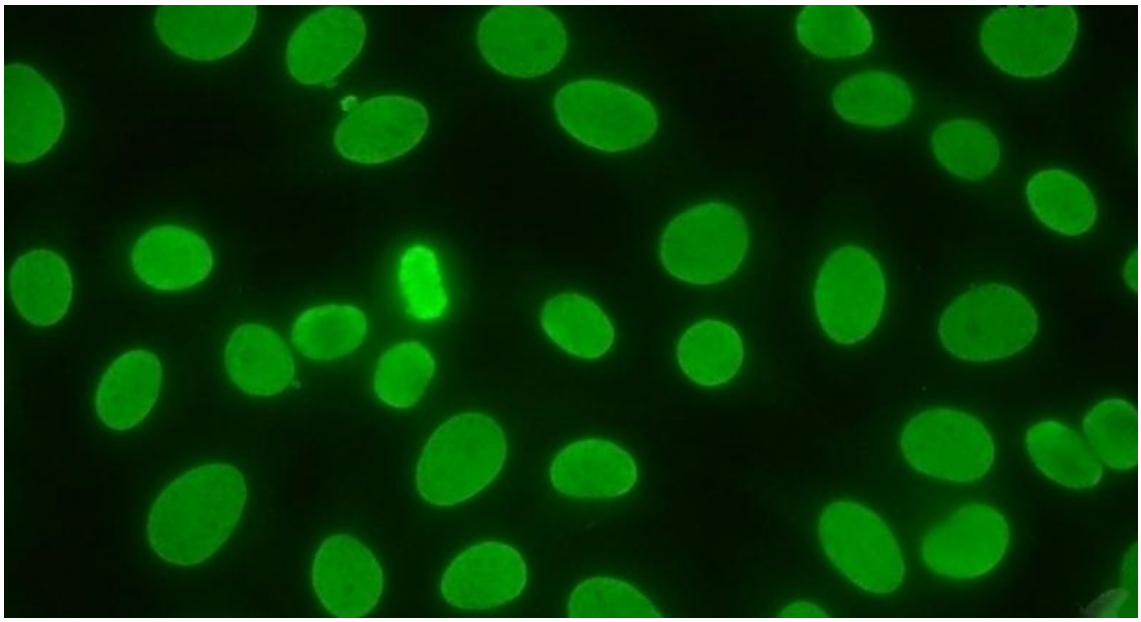
Nature of Antigen	Antibody System	Disease, %Positive					
		SLE	Drug-Induced LE	Systemic Sclerosis—Diffuse	Limited Scleroderma—CREST	Sjögren Syndrome	Inflammatory Myopathies
Many nuclear antigens (DNA, RNA, proteins)	Generic ANA (indirect IF)	>95	>95	70–90	70–90	50–80	40–60
Native DNA	Anti–double-stranded DNA	40–60	<5	<5	<5	<5	<5
Histones	Antihistone	50–70	>95	<5	<5	<5	<5
Core proteins of small nuclear RNP particles (Smith antigen)	Anti-Sm	20–30	<5	<5	<5	<5	<5
RNP (U1RNP)	Nuclear RNP	30–40	<5	15	10	<5	<5
RNP	SS-A(Ro)	30–50	<5	<5	<5	70–95	10
RNP	SS-B(La)	10–15	<5	<5	<5	60–90	<5
DNA topoisomerase I	Scl-70	<5	<5	28–70	10–18	<5	<5
Centromeric proteins	Anticentromere	<5	<5	22–36	90	<5	<5
Histidyl-tRNA synthetase	Jo-1	<5	<5	<5	<5	<5	25

Antinuclear antibody (ANA):

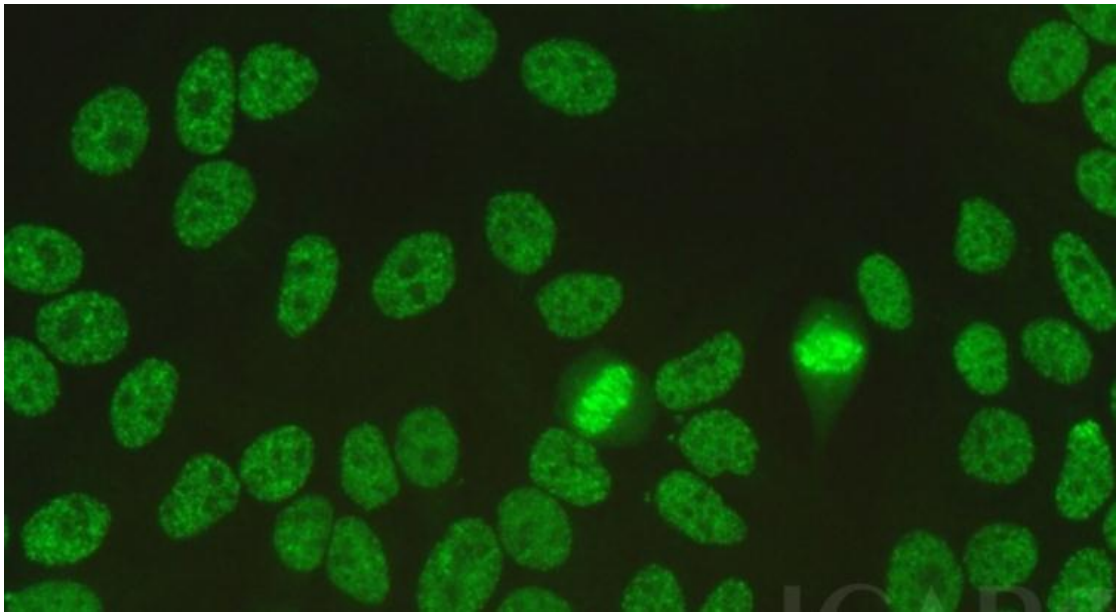
Immunoglobulins of all classes may form Antinuclear antibody. There are several morphological patterns of immunoflorescent staining.

- Peripheral pattern is characteristic of active disease
- Speckled pattern denotes antibodies directed against non DNA nuclear constituents.
- Nucleolar pattern stains ribosomal precursor of Ribonucleoprotein

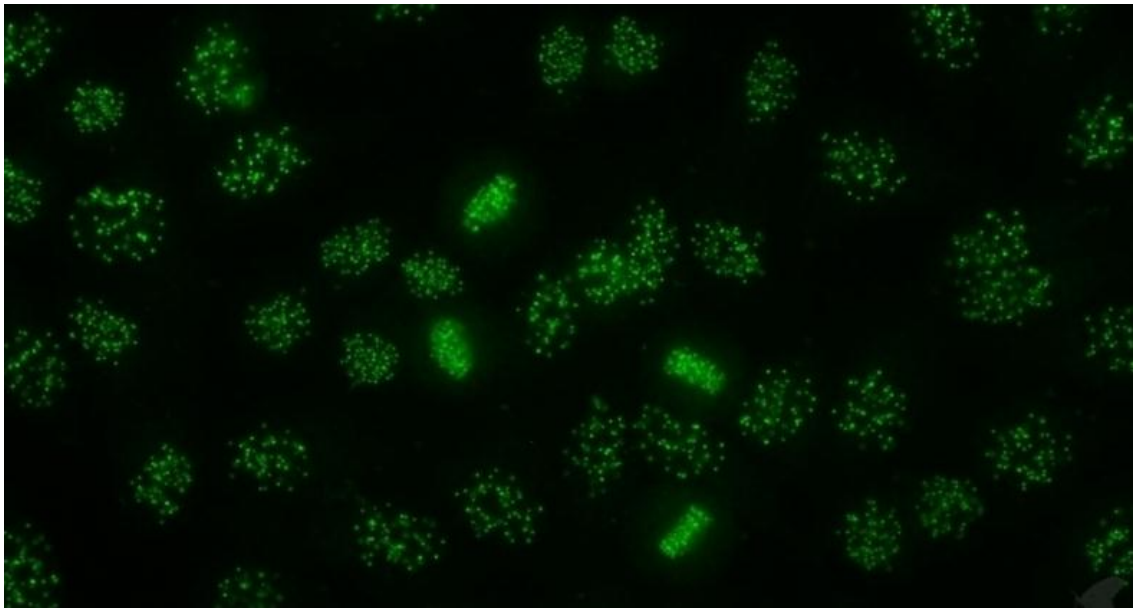
Homogenous pattern –



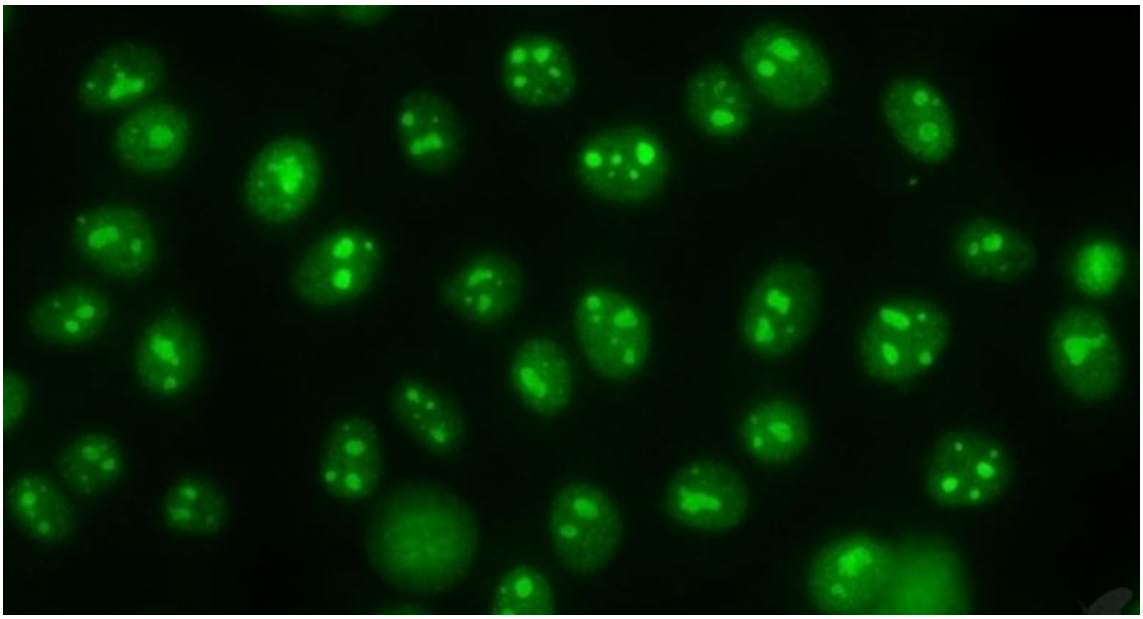
Speckled pattern –



Centromere pattern –



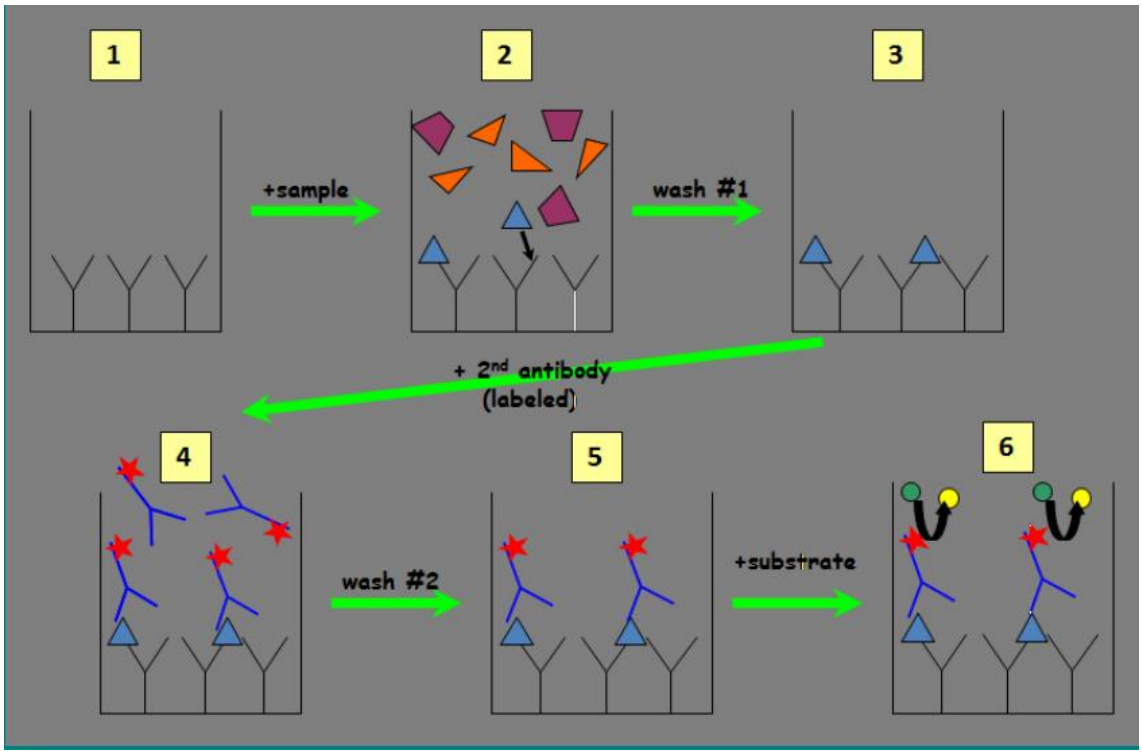
Nucleolar pattern –



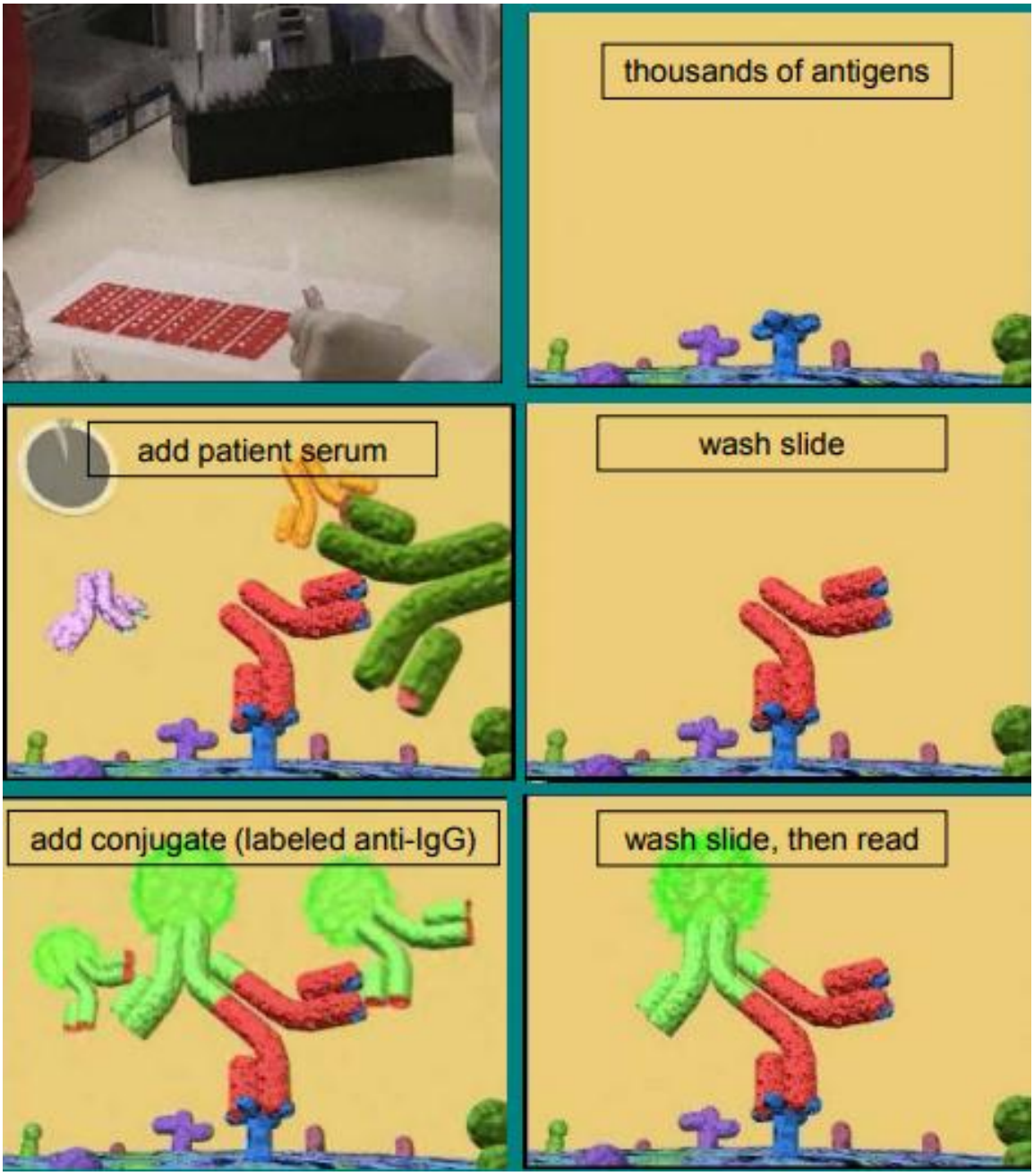
The pattern of ANA positivity has to be interpreted with caution because:

- Serum of patients with any rheumatic disease may contain autoantibodies to different nuclear constituents so that homogenous pattern may obscure a speckled or nucleolar pattern.
- Different antibodies in serum can be present in different titers, so that by diluting the serum, the observed pattern can be changed.
- Stability of different antigens is different and can be changed by fixation or denaturation.
- The types of tissues or cells used as substrate for the test also influences the pattern.

Technique of ELISA:



Technique of Indirect Immunofluorescence:



Mycobacterium tuberculosis

TB burden:

Estimates of TB Burden (2015)	Global	India
Incidence TB cases	104 lakh	28 Lakh
Mortality of TB	14 lakh	4.8 lakh
Incidence HIV TB	11.7 lakh	1.1 lakh
Mortality of HIV-TB	3.9 lakh	37,000
MDR-TB	4.8 lakh	1.3 lakh

Antigenic structure of Mycobacterium tuberculosis:

- Cell wall (insoluble antigens)
    - Peptidoglycan layer – maintains shape and rigidity of the cell.
    - Arabinogalactan layer - facilitates survival within the macrophages
    - Mycolic acid layer – Long chain Fatty Acid attached to arabinogalactan and confers very low permeability to cell wall. It is also responsible for the acid fastness and the reduced entry of most antibiotics.
    - Outermost layer – contains lipids (mycocerosates and acylglycerols), glycolipids and mycosides (phenolic glycolipids).
    - Proteins – porins, Transport proteins

- Plasma membrane – includes proteins, phosphatidylinositol, mannosides and lipoarabinomannans

- Cytoplasmic (soluble) antigens
    - Ag 5, 6, 60
    - They are used in serodiagnosis of tuberculosis

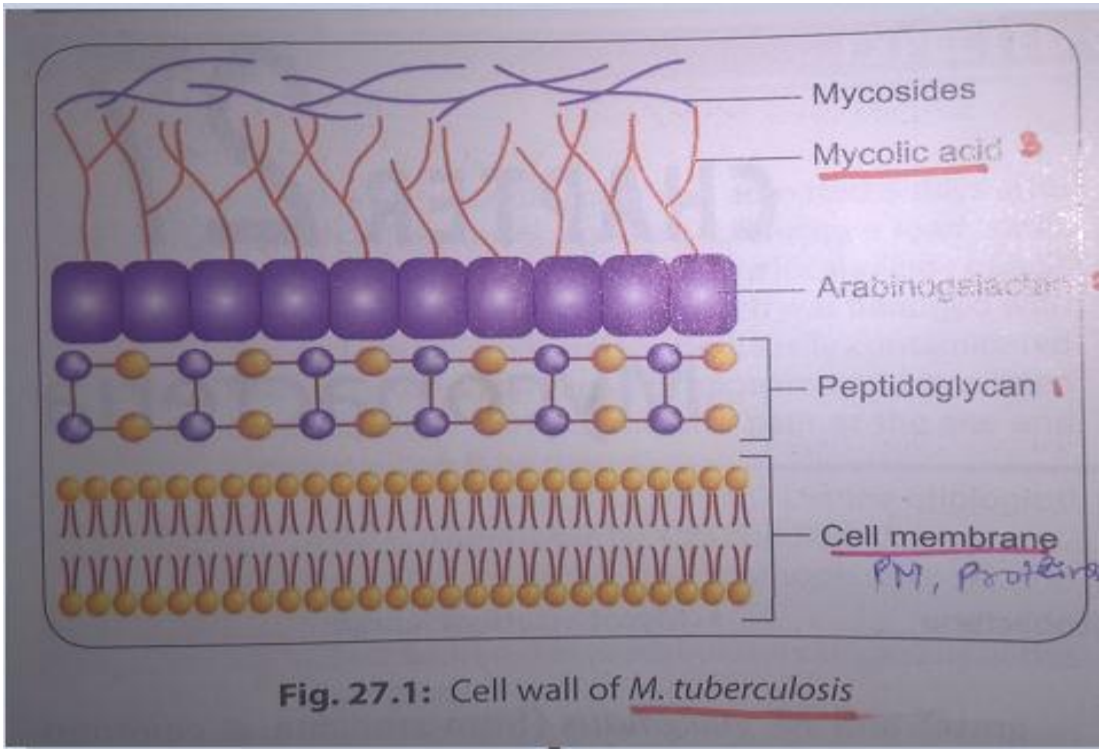


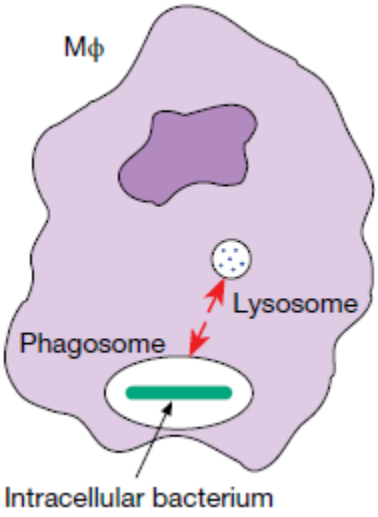
Fig. 27.1: Cell wall of *M. tuberculosis*

Sequence of pathogenic events:

- Spread through droplet nuclei; about < 10 % reach alveoli whereas others are removed by mucociliary clearance

- Adhesion to macrophages: Lipoarabinomannan (LAM) binds to complement receptors and mannose receptors on the surface of macrophages. This leads to internalization of bacilli.
- Phagocytosis by macrophages is increased by C3b mediated opsonisation.
- Survival inside macrophages: LAM impairs phagolysosome fusion by inhibiting increase in intracellular calcium and phosphatidylinositol-3-P
- Replicates inside phagolysosome
- Macrophage ruptures and releases bacillary contents
- Released bacilli infects other phagocytes.

Inhibition of phagolysosome fusion by Mycobacterium tuberculosis



Host immune response against Mycobacteria tuberculosis:

Cell mediated immunity :

- Macrophages present the mycobacterial antigens to T- helper cells
- T helper cells of 1 subset secretes IL 2 and Interferon gamma
- IL 2 and IFN gamma activates macrophages and monocytes
- Macrophage activating response : Activated macrophages are capable of killing and digesting tubercle bacilli
- Tubercle formation: growth of bacilli is inhibited within the necrotic environment because of low oxygen tension and low pH. Viable bacilli may remain dormant for many years.
- Tissue damaging response: Occurs in minority of cases. Macrophage activating response is weak and bacilli are more virulent. Mycobacterial growth can be inhibited only by Delayed type hypersensitivity reaction which leads to lung tissue destruction.

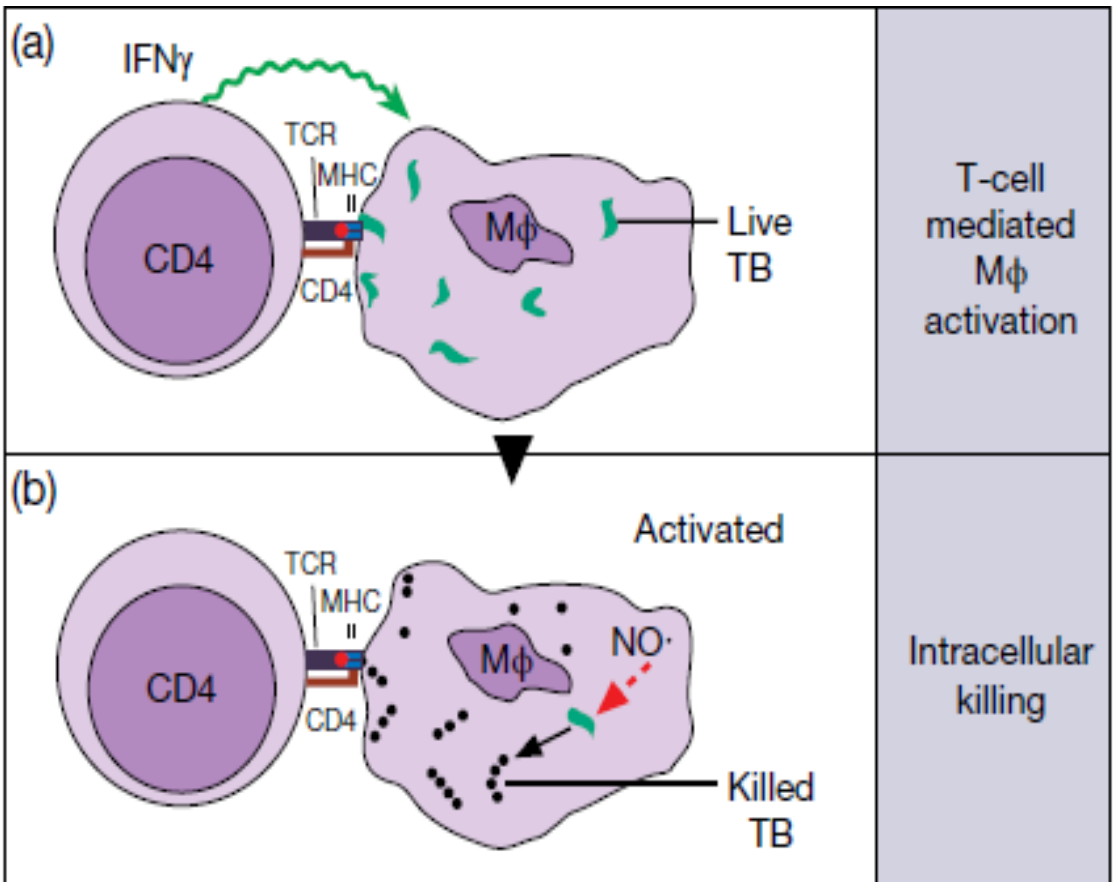
Humoral response :

- T helper cells of 2 subset secretes IL 4 and IL 5
- Activates B cells
- Antibodies are produced which play a minor role because mycobacterium tuberculosis is an obligate intracellular organism.
- Anti LAM prevents TB dissemination in children.

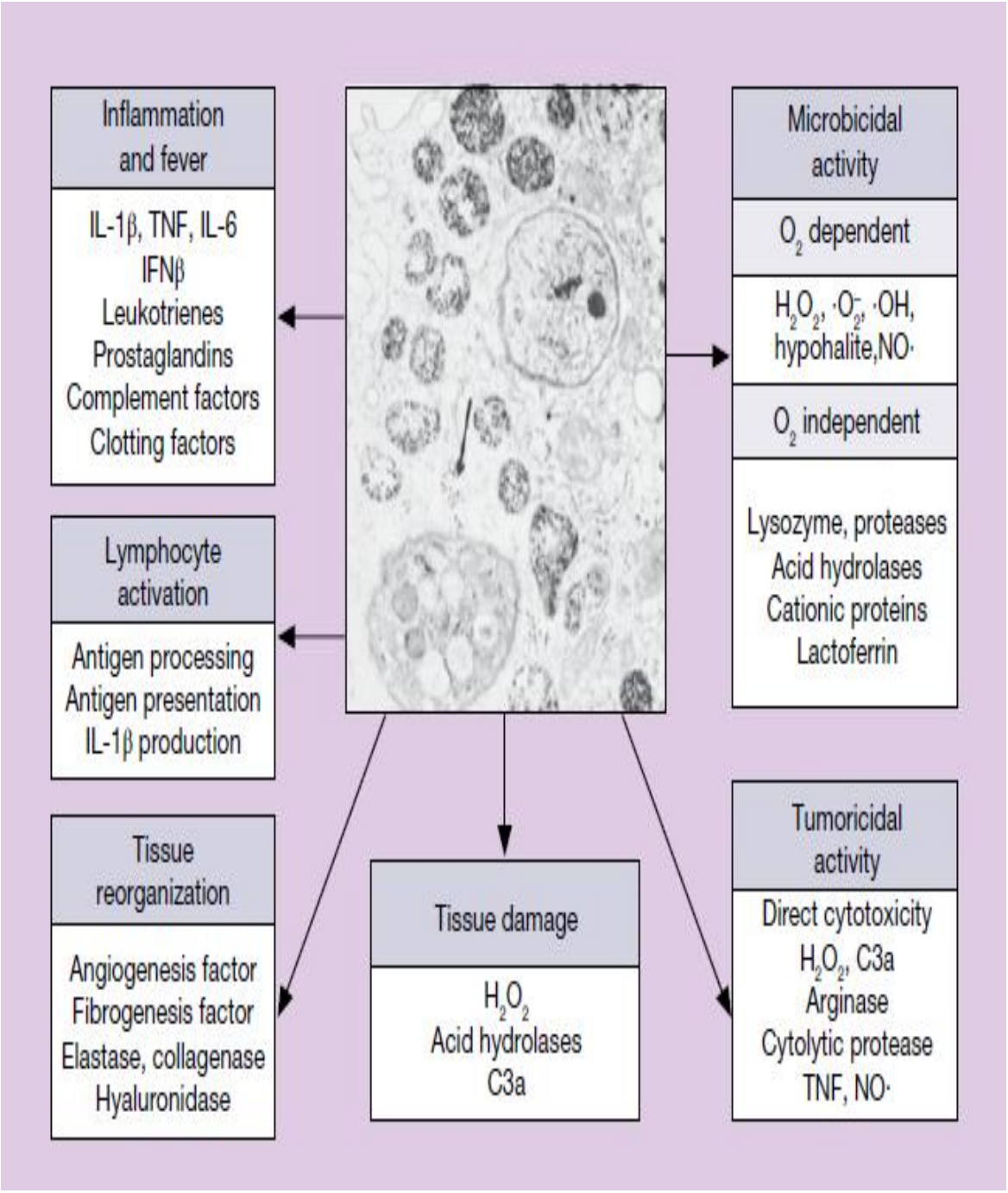
T cell mediated killing of Mycobacteria by macrophages:

Mycobacterial peptides associated with MHC Class II cells is recognized by specialized CD4 TH1 cells thereby releasing macrophage activating Interferon gamma.

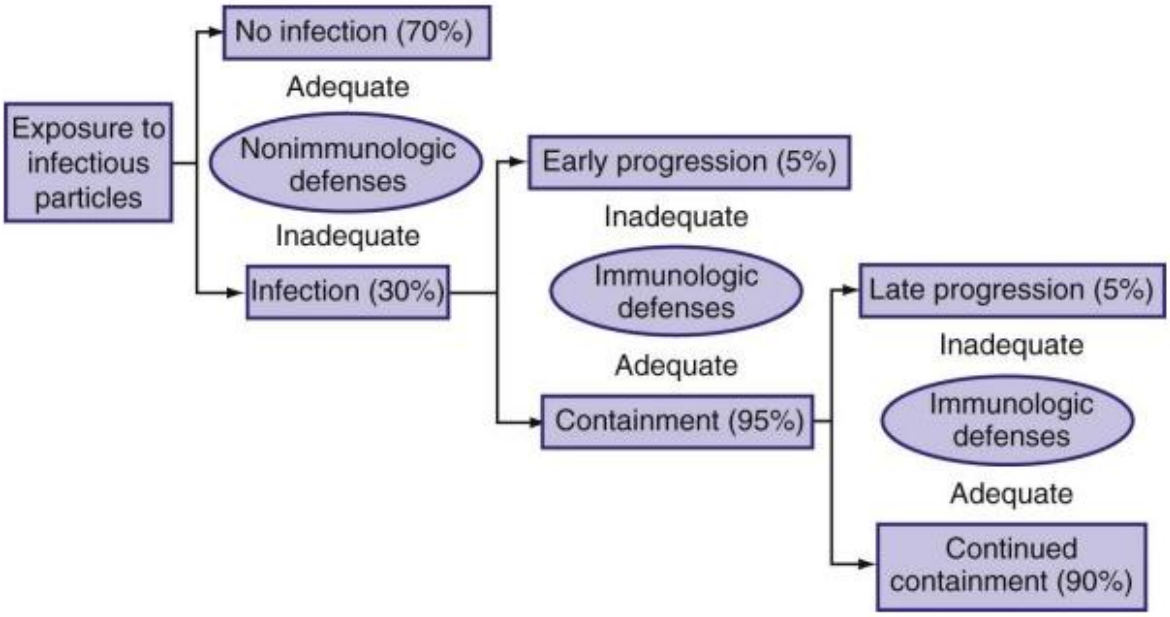
The activated macrophages generates NO thereby killing the intracellular tubercle bacilli.



Role of macrophages:



Consequences of exposure to an infectious source case of tuberculosis:



Clinical features of Tuberculosis:

- Pulmonary TB : 80% of all cases
- TB lymphadenitis : 35 % of all EPTB
- Pleural TB : 20% of all EPTB
- TB of upper airways : Larynx, pharynx, epiglottis
- Genitourinary TB : Kidneys, epididymis, Fallopian tube and endometrium
- Skeletal TB
- CNS TB : meningitis, tuberculomas
- GIT : terminal ileum and caecum commonly involved
- Pericarditis

- Skin : scrofuloderma, Lupus vulgaris, scrofula, Erythema nodosum, Tuberculous Verrucosa cutis, Lichen scrofulosorum, Papulonecrotic tuberculid
- Military TB

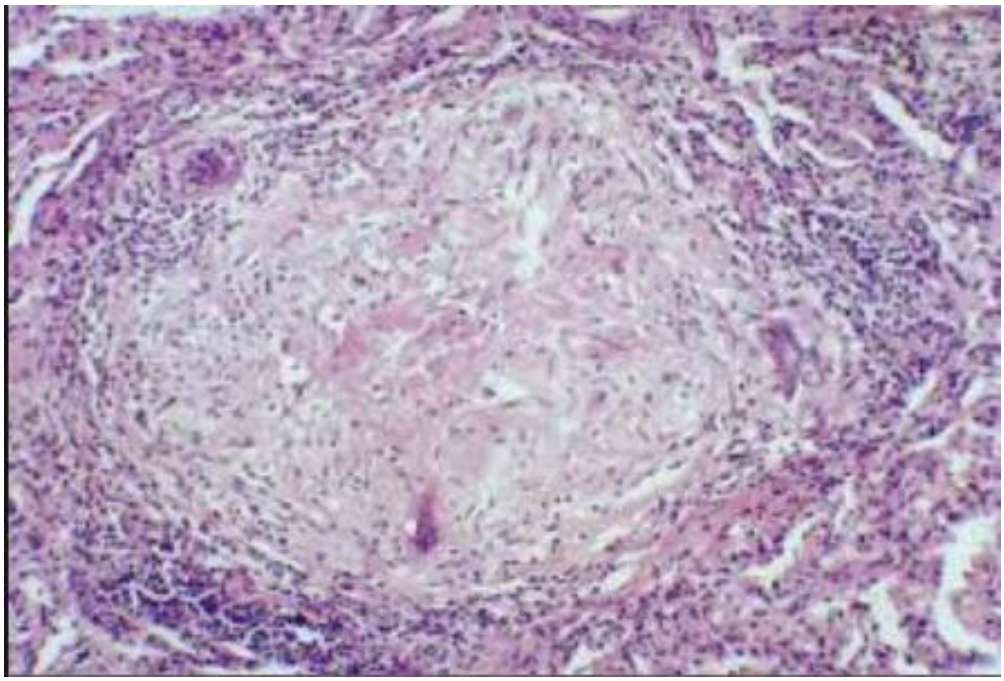
X ray image of Pleural effusion:

X ray image of Fibrocavity :

X ray image of Miliary TB:

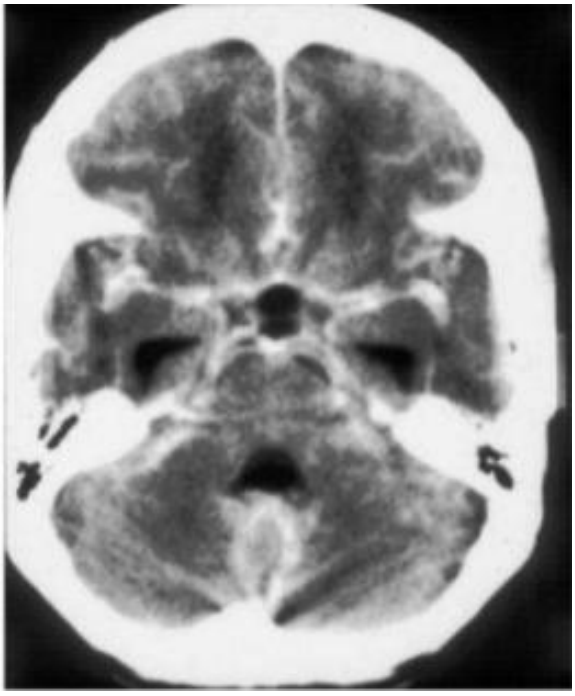
X ray image of consolidation:

HPE showing caseating granuloma :



Contrast CT of tuberculoma brain:

Contrast CT of brain with TB meningitis and dilatation of ventricles :



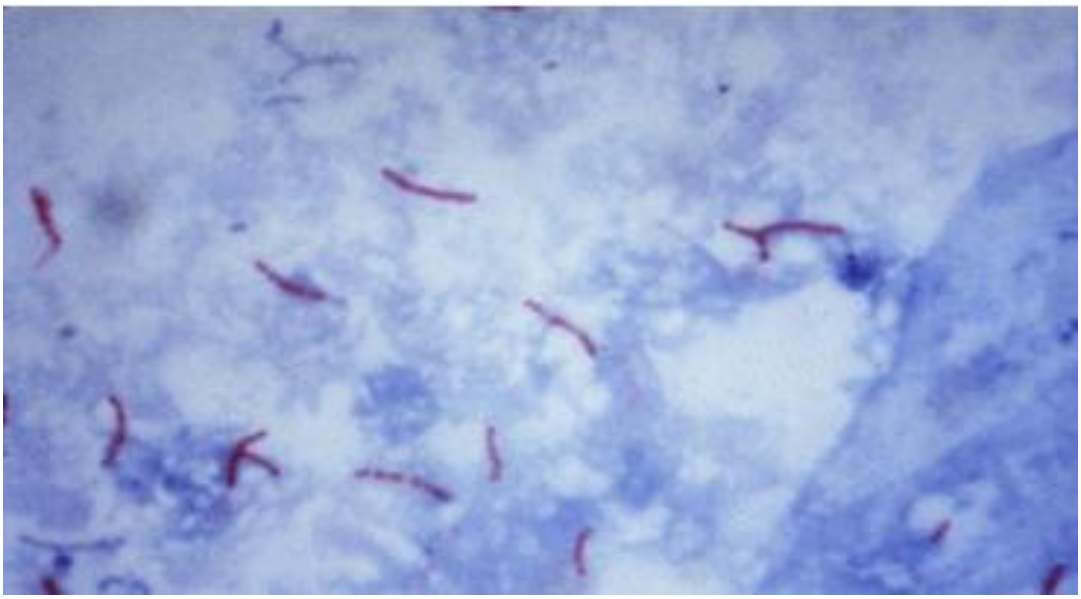
MRI image of Potts spine:

Demonstration of TB bacilli by AFB stain:

The characteristic feature of true tubercle bacilli is "acid-fastness"- the bacilli resists decoloration by 95% ethyl alcohol with 3% hydrochloric acid. Waxy envelope integrity is responsible for the acid fastness. The acid-fast bacteria is identified by Ziehl-Neelsen technique of staining.

Technique of Ziehl-Neelsen staining:

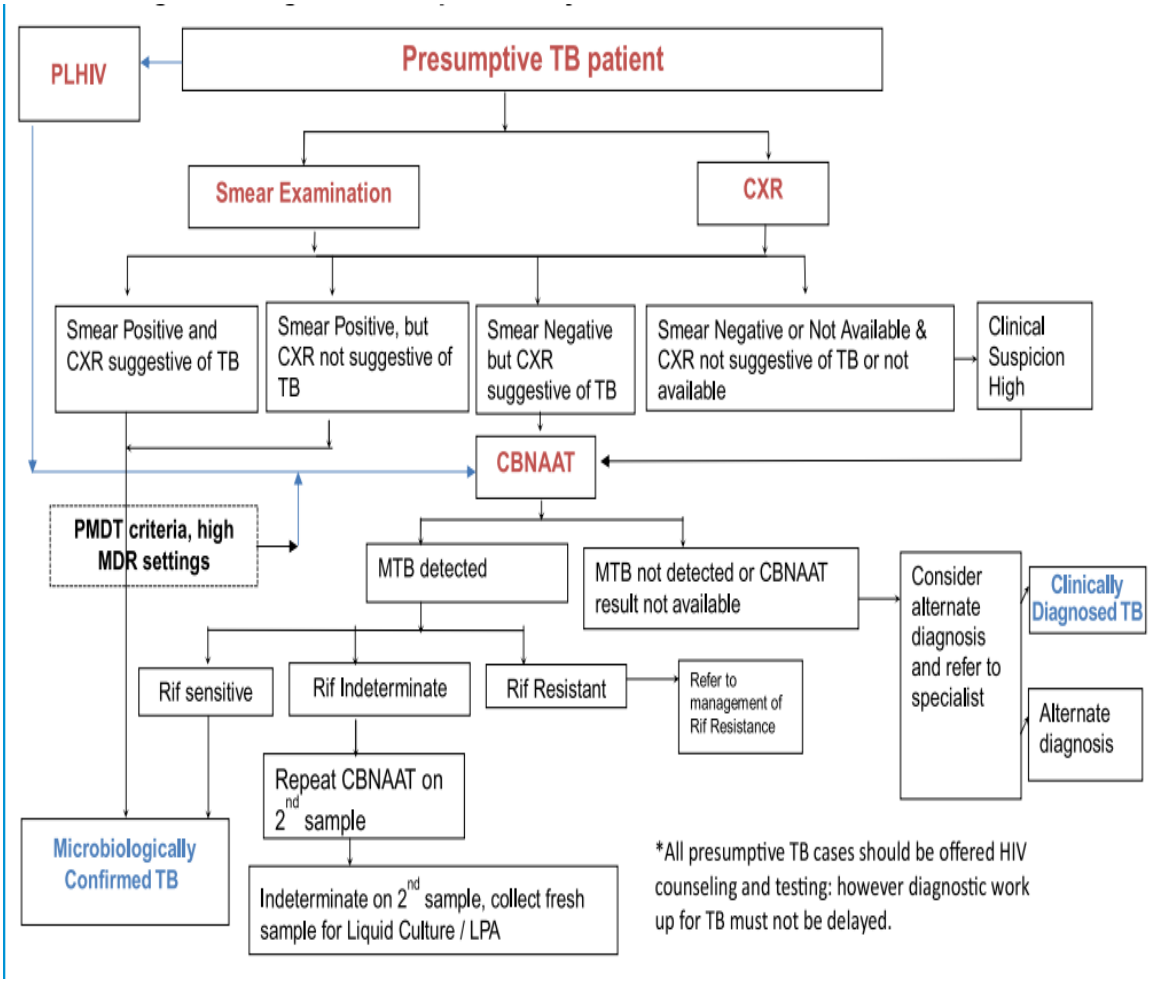
(1) Fix smear by heat.
(2) Cover with carbolfuchsin, steam gently for 5 minutes over direct flame (or for 20 minutes over a water bath).
(3) Wash with water.
(4) Decolorize in acid-alcohol until only a faint pink color remains.
(5) Wash with water.
(6) Counterstain for 10–30 seconds with Loeffler's methylene blue.
(7) Wash with water and let dry.



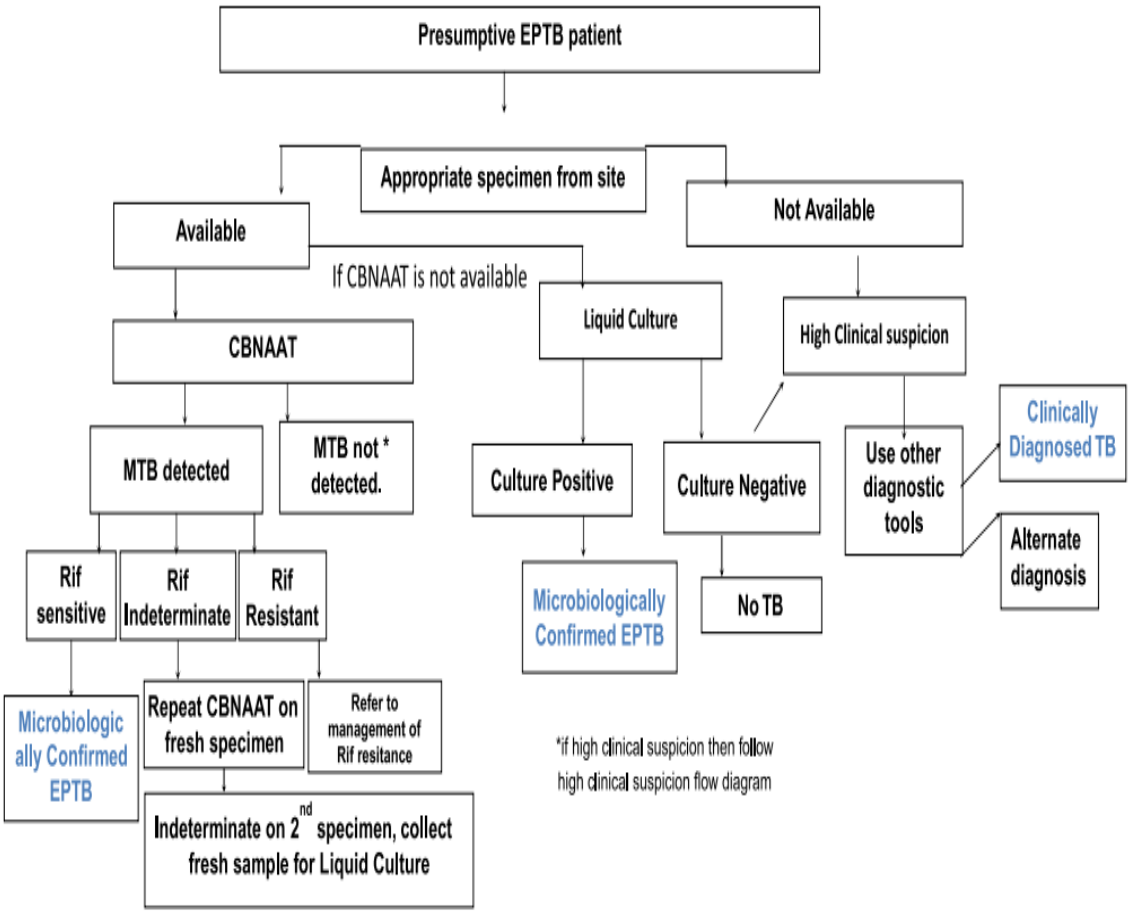
RNTCP guidelines for grading sputum by ZN stain:

NO. of bacilli seen	Grading	No. of OIF to be screened
10/OIF	3+	20
1-10 / OIF	2+	50
10 – 99/ 100 OIF	1+	100
1 -9/ 100 OIF	Scanty	100
No AFB in 100 OIF	Nil	100

Diagnostic algorithm for Pulmonary TB:



Diagnostic algorithm for Extrapulmonary TB:



Treatment of Tuberculosis:

- Presumptive Pulmonary TB : A patient with any symptoms/signs suggestive of TB like cough for 2 weeks, fever for 2 weeks, significant weight loss, hemoptysis and X ray abnormality
- Presumptive Extrapulmonary TB: Presence of organ specific symptoms/signs and/or constitutional symptoms like weight loss, fever for 2 weeks and night sweats.
- Microbiologically confirmed case: Presumptive TB patient with biological specimen positive for AFB/ culture / quality assured rapid diagnostic molecular test.
- Clinically confirmed case ; Presumptive TB patient, not microbiologically confirmed but diagnosed with active TB based on X ray abnormality, HPE and signs with a decision by a clinician to treat with full course of ATT.
- New case: A TB patient who has never been treated for TB or has taken ATT for less than one month.
- Recurrent TB case: A TB patient previously declared as successfully treated and is subsequently found to be a microbiologically confirmed TB case.

- Treatment failure: Patient who has been previously treated for TB and whose treatment has failed at the end of their most recent treatment course.

Type of TB Case	Treatment regimen in IP	Treatment regimen CP
New	(2) HRZE	(4) HRE
Previously treated	(2) HRZES + (1) HRZE	(5) HRE

Prefix to the drugs stands for number of months

MATERIALS AND METHODS

MATERIALS AND METHODS

Study center:

Institute of Internal Medicine,

Madras Medical College & Rajiv Gandhi Government General Hospital,

Chennai – 3.

Study Design:

Single center observational prospective study

Sample size:

100 consecutive Tuberculosis patients attending Thoracic Medicine department or Internal medicine department based on inclusion and exclusion criteria.

Collaborating Departments:

- Institute of Rheumatology, MMC&RGGGH, Ch-3
- Institute of Thoracic medicine, MMC & RGGGH, Ch-3
- Institute of Biochemistry, MMC & RGGGH, Ch – 3

Study Duration:

- Study was conducted from March 2017-August 2017

Study Plan:

Based on prior studies, the prevalence of ANA in patients with TB was about 33%[45], hence the required sample size based on the formula 4 (prevalence of disease) (1- prevalence of disease) / Error range (5-15) was about 80. About 100 Patients attending Thoracic Medicine and Internal Medicine OPD or admitted in the wards were subjected to detailed history taking, clinical examination and blood investigations like CBC, Renal function tests, Liver function tests, HIV, HBsAg and Anti-HCV. Chest X ray, Sputum / tissue/ fluid AFB, Sputum / tissue/ fluid gene expert analysis was done depending on the diagnosis. Immunological testing for ANA (Antinuclear Antibody) by ELISA method was done for all the patients. Those who were found to be ANA positive underwent ANA profiling for detecting specific autoantibody

Inclusion criteria:

- Newly detected pulmonary and extrapulmonary tuberculosis patients.

Exclusion criteria:

1. Patients with known Connective Tissue Disorders
2. Patients with drug induced CTD
3. Patients with Chronic Kidney Disease

4. Patients with Chronic Liver Disease

5. Age < 20 and > 50 years

6. DM

7. HIV

Statistical Analysis Plan:

Data analysed using statistical package - SPSS Software

Consent

All participants / attenders gave written informed consent.

Ethical Committee Approval

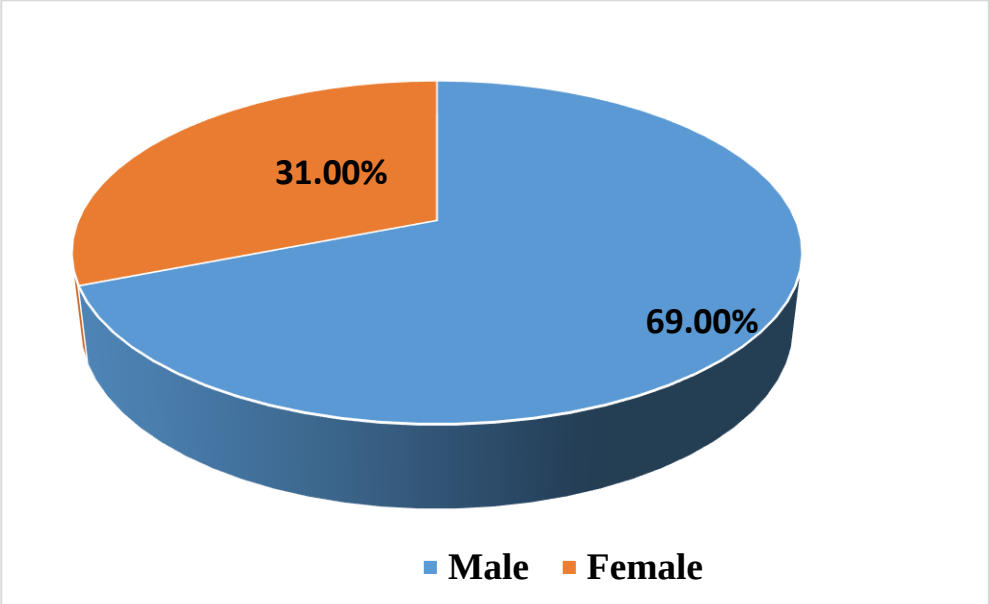
Institutional Ethics Committee of Madras Medical College approved the study.

OBSERVATION AND RESULTS

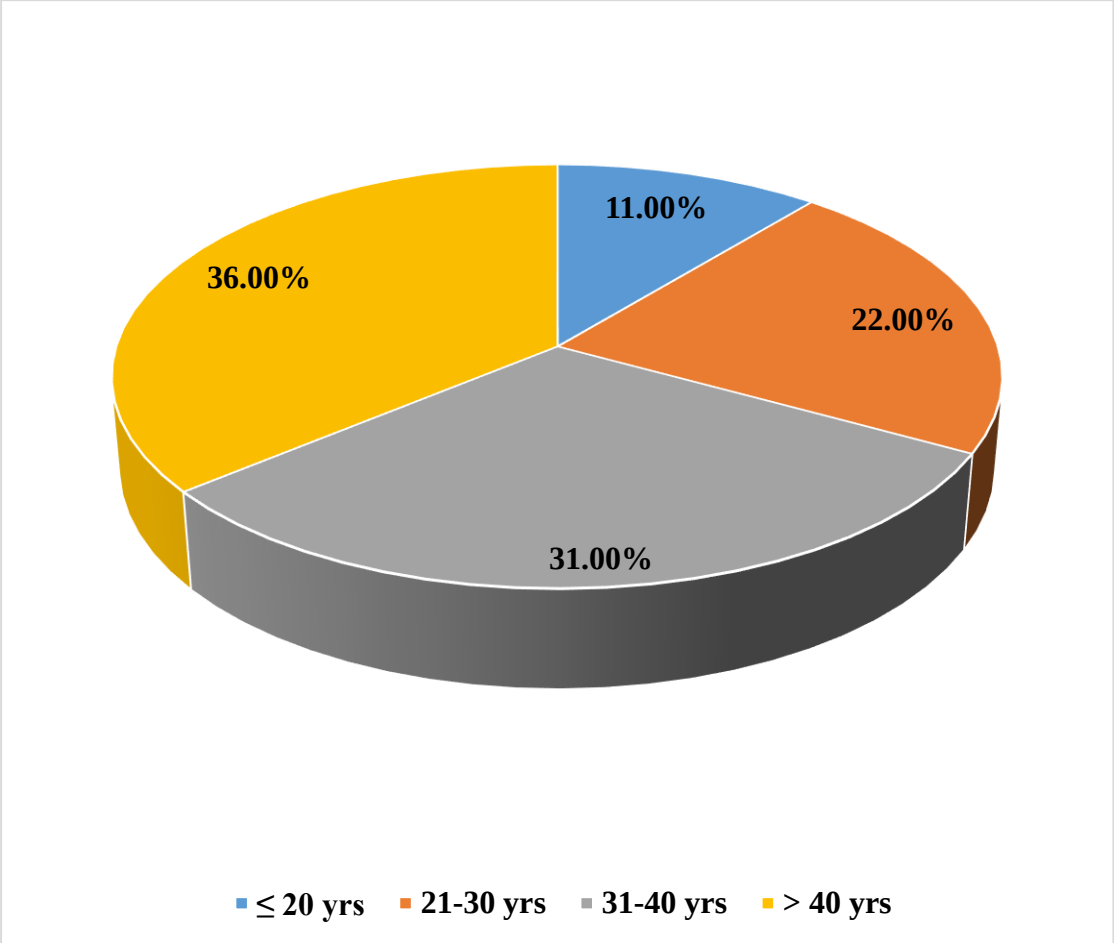
OBSERVATION AND RESULTS

In the study of 100 patients of Tuberculosis in Madras Medical College & Rajiv Gandhi Govt. General Hospital, Chennai, the following observations were made in sex incidence, age, Pulmonary/ Extra pulmonary TB, duration of illness, sputum AFB positivity, ANA positivity and ANA profiling.

Gender	N	%
Male	69	69.0%
Female	31	31.0%
Total	**100**	**100.0%**

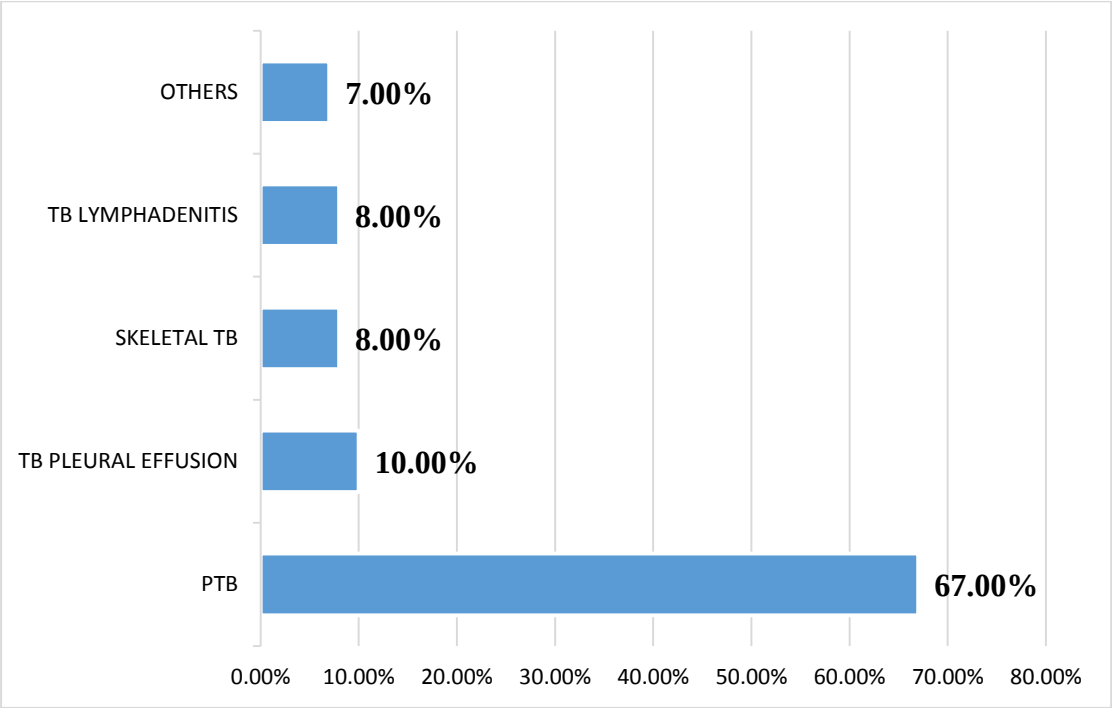


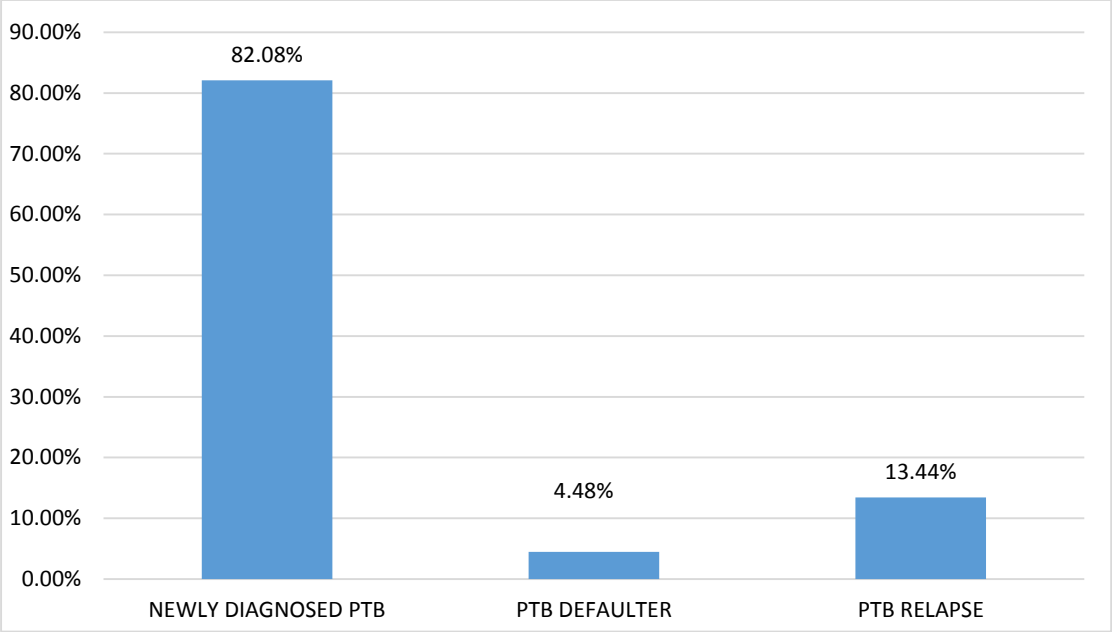
Age group	N	%
≤ 20 yrs	11	11.0%
21-30 yrs	22	22.0%
31-40 yrs	31	31.0%
> 40 yrs	36	36.0%
Total	**100**	**100.0%**



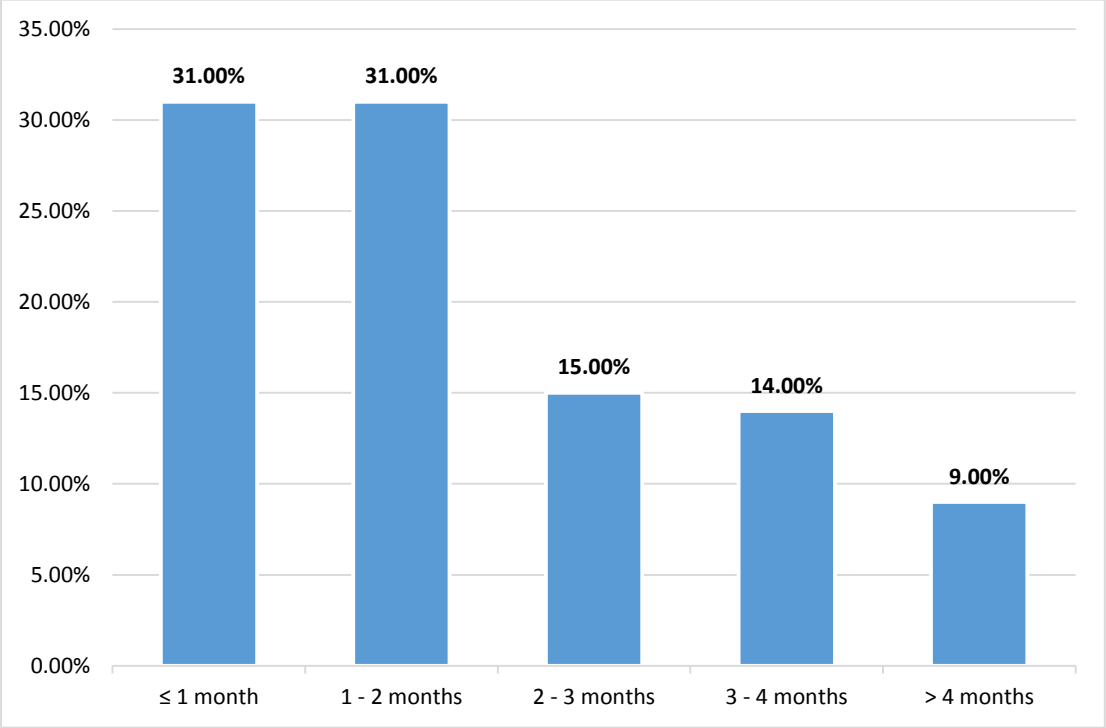
Diagnosis	N	%
ABDOMINAL TB	1	1.0%
COLD ABSCESS CHEST WALL	1	1.0%
DISSEMINATED TB	1	1.0%
ILEOCAECAL TB	1	1.0%
LUPUS VULGARIS	1	1.0%
OCULAR TB	2	2.0%
PTB	53	53.0%
PTB / LARYNGEAL TB	1	1.0%
PTB DEFAULTER	2	2.0%
PTB DEFAULTER / 7 MONTHS ANTENATAL	1	1.0%
PTB RELAPSE	9	9.0%
PTB/ OLD CVA	1	1.0%
SACRAL TB OSTEOMYELITIS	1	1.0%
SPINAL TB	3	3.0%
TB LYMPHADENITIS	8	8.0%
TB OSTEOMYELITIS	2	2.0%
TB PLEURAL EFFUSION	10	10.0%
TB SACROILITIS	1	1.0%
TB SPONDYLODISCITIS	1	1.0%
Total	100	100.0%

Diagnosis	N	%
Pulmonary TB	67	67.0%
Extra PTB	33	33.0%
Total	100	100.0%

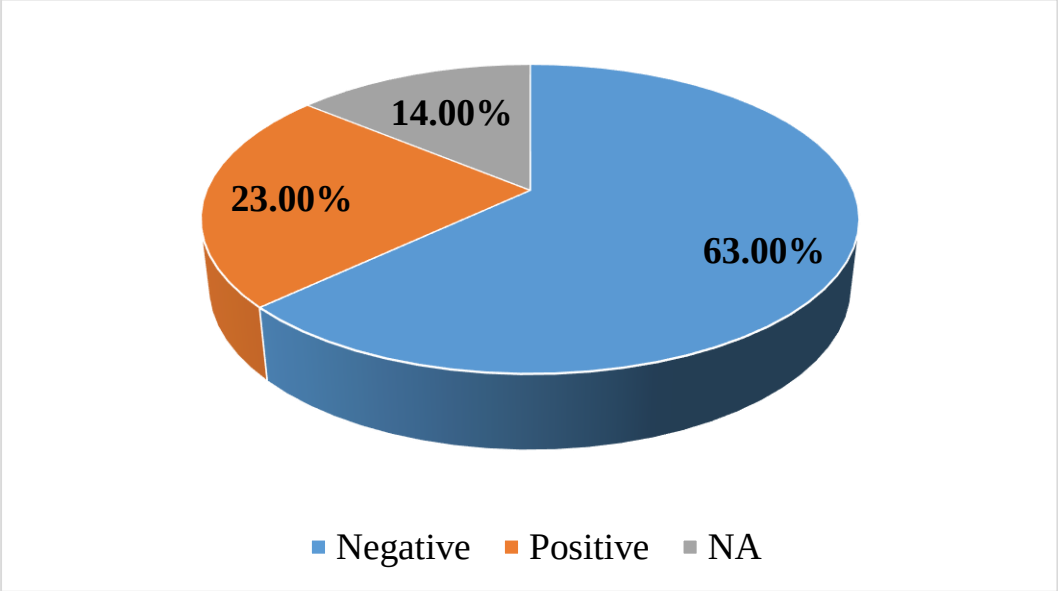

OTHERS
7.00%
TB LYMPHADENITIS
8.00%
SKELETAL TB
8.00%
TB PLEURAL EFFUSION
10.00%
PTB
67.00%
0.00%
10.00%
20.00%
30.00%
40.00%
50.00%
60.00%
70.00%
80.00%


90.00%
80.00%
70.00%
60.00%
50.00%
40.00%
30.00%
20.00%
10.00%
0.00%
82.08%
4.48%
13.44%
NEWLY DIAGNOSED PTB
PTB DEFAULTER
PTB RELAPSE

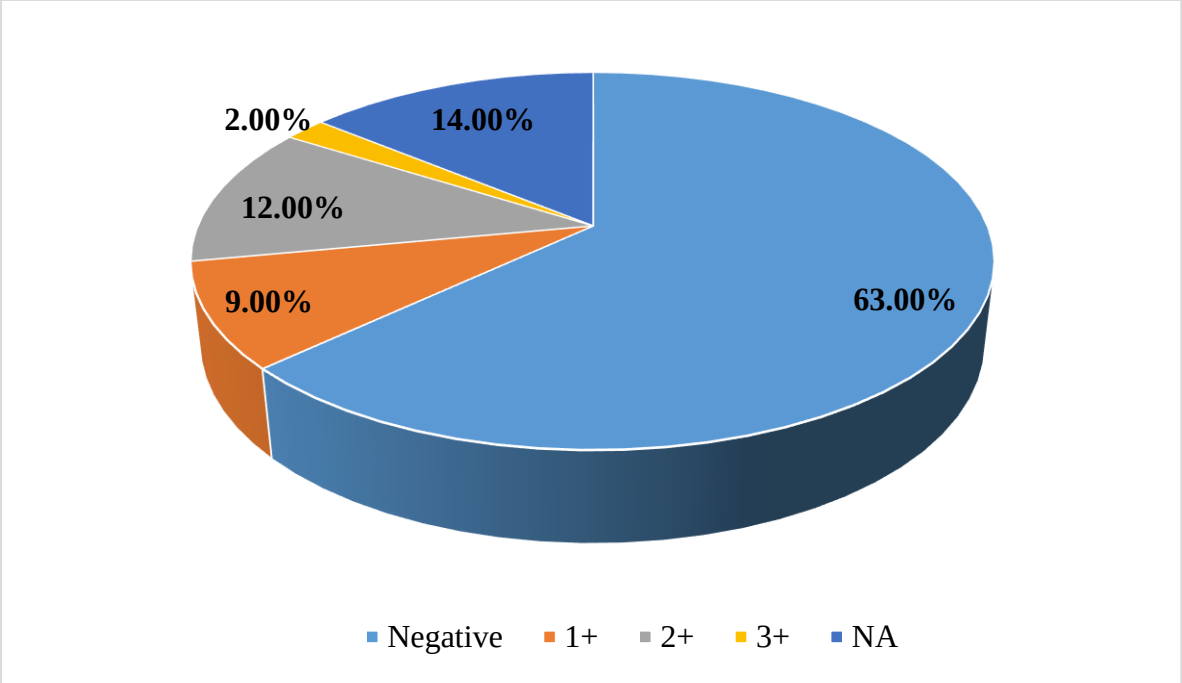
Duration of illness	N	%
≤ 1 month	31	31.0%
1 - 2 months	31	31.0%
2 - 3 months	15	15.0%
3 - 4 months	14	14.0%
> 4 months	9	9.0%
Total	100	100.0%



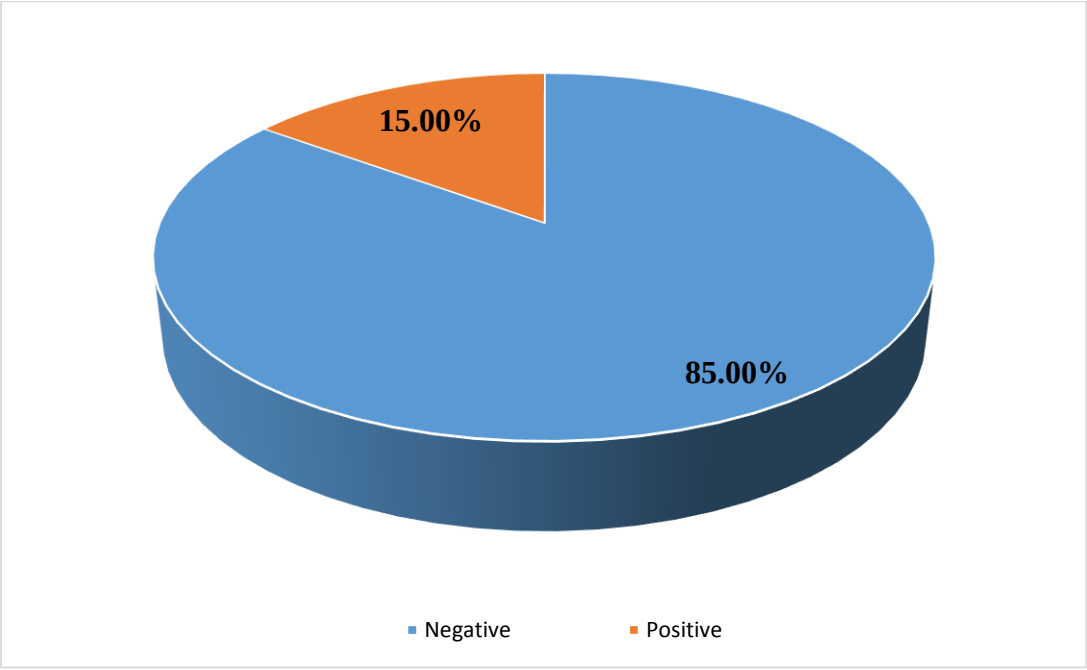
Sputum AFB	N	%
Negative	63	63.0%
Positive	23	23.0%
NA	14	14.0%
Total	100	100.0%



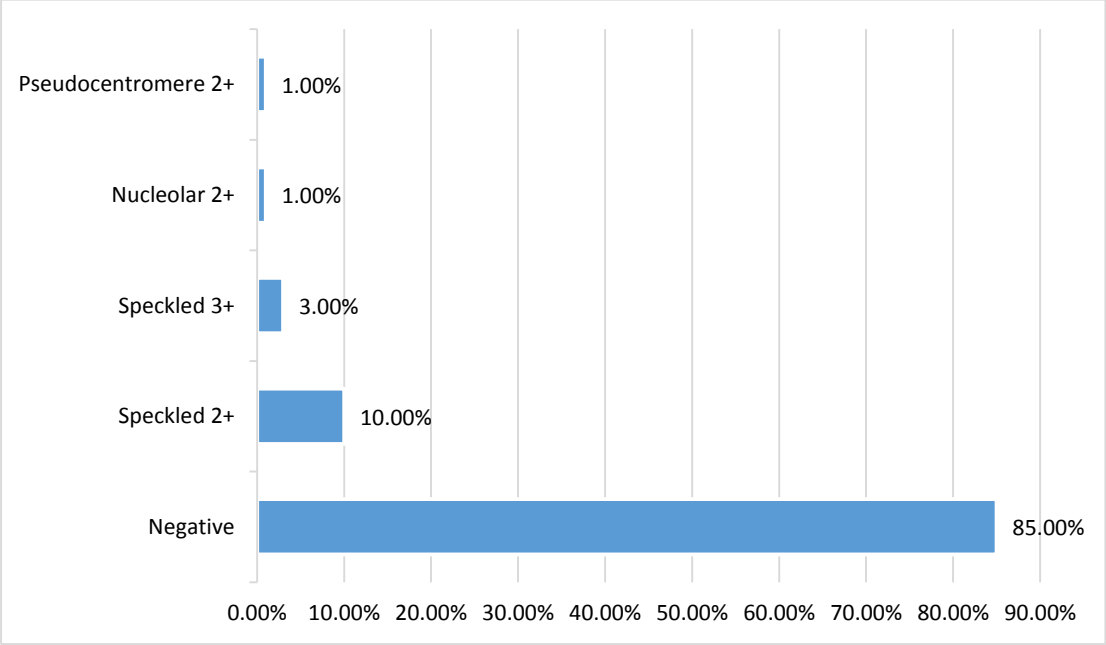
Sputum AFB	N	%
Negative	63	63.0%
1+	9	9.0%
2+	12	12.0%
3+	2	2.0%
NA	14	14.0%
Total	100	100.0%



ANA Report	N	%
Negative	85	85.0%
Positive	15	15.0%
Total	100	100.0%



ANA Report	N	%
Negative	85	85.0%
Speckled 2+ pattern	10	10.0%
Speckled 3+ pattern	3	3.0%
Nucleolar 2+ pattern	1	1.0%
Pseudo centromere 2+ pattern	1	1.0%
Total	100	100.0%



Cross Tables

Diagnosis	Gender			
	Male		Female	
	N	%	N	%
ABDOMINAL TB	0	0.0%	1	3.2%
COLD ABSCESS CHEST WALL	1	1.4%	0	0.0%
DISSEMINATED TB	1	1.4%	0	0.0%
ILEOCAECAL TB	1	1.4%	0	0.0%
LUPUS VULGARIS	1	1.4%	0	0.0%
OCULAR TB	1	1.4%	1	3.2%
PTB	37	53.6%	16	51.6%
PTB / LARYNGEAL TB	0	0.0%	1	3.2%
PTB DEFAULTER	2	2.9%	0	0.0%
PTB DEFAULTER / 7 MONTHS ANTENATAL	0	0.0%	1	3.2%
PTB RELAPSE	7	10.1%	2	6.5%
PTB/ OLD CVA	1	1.4%	0	0.0%
SACRAL TB OSTEOMYELITIS	0	0.0%	1	3.2%
SPINAL TB	3	4.3%	0	0.0%
TB LYMPHADENITIS	3	4.3%	5	16.1%
TB OSTEOMYELITIS	1	1.4%	1	3.2%
TB PLEURAL EFFUSION	8	11.6%	2	6.5%
TB SACROILITIS	1	1.4%	0	0.0%
TB SPONDYLODISCITIS	1	1.4%	0	0.0%
Total	69	100.0%	31	100.0%

P-Value = 0.357 (NS)

Diagnosis	Age group							
	≤ 20 yrs		21-30 yrs		31-40 yrs		> 40 yrs	
	N	%	N	%	N	%	N	%
ABDOMINAL TB	0	0.0%	1	4.5%	0	0.0%	0	0.0%
COLD ABSCESS CHEST WALL	0	0.0%	1	4.5%	0	0.0%	0	0.0%
DISSEMINATED TB	0	0.0%	1	4.5%	0	0.0%	0	0.0%
ILEOCAECAL TB	0	0.0%	0	0.0%	0	0.0%	1	2.8%
LUPUS VULGARIS	0	0.0%	1	4.5%	0	0.0%	0	0.0%
OCULAR TB	1	9.1%	1	4.5%	0	0.0%	0	0.0%
PTB	5	45.5%	8	36.4%	20	64.5%	20	55.6%
PTB / LARYNGEAL TB	0	0.0%	1	4.5%	0	0.0%	0	0.0%
PTB DEFAULTER	0	0.0%	0	0.0%	2	6.5%	0	0.0%
PTB DEFAULTER / 7 MONTHS ANTENATAL	0	0.0%	1	4.5%	0	0.0%	0	0.0%
PTB RELAPSE	0	0.0%	0	0.0%	3	9.7%	6	16.7%
PTB/ OLD CVA	0	0.0%	0	0.0%	0	0.0%	1	2.8%
SACRAL TB OSTEOMYELITIS	0	0.0%	0	0.0%	1	3.2%	0	0.0%
SPINAL TB	1	9.1%	0	0.0%	1	3.2%	1	2.8%
TB LYMPHADENITIS	3	27.3%	3	13.6%	1	3.2%	1	2.8%
TB OSTEOMYELITIS	0	0.0%	1	4.5%	0	0.0%	1	2.8%
TB PLEURAL EFFUSION	0	0.0%	3	13.6%	2	6.5%	5	13.9%
TB SACROILITIS	1	9.1%	0	0.0%	0	0.0%	0	0.0%
TB SPONDYLODISCITIS	0	0.0%	0	0.0%	1	3.2%	0	0.0%
Total	11	100.0%	22	100.0%	31	100.0%	36	100.0%

P-Value = 0.093 (NS)

Gender	Diagnosis					
	Pulmonary TB		Extra PTB		Total	
	N	%	N	%	N	%
Male	47	70.1%	22	66.7%	69	69.0%
Female	20	29.9%	11	33.3%	31	31.0%
Total	67	100.0%	33	100.0%	100	100.0%

P-Value = 0.723 (NS)

Age group	Diagnosis					
	Pulmonary TB		Extra PTB		Total	
	N	%	N	%	N	%
≤ 20 yrs.	5	7.5%	6	18.2%	11	11.0%
21-30 yrs	10	14.9%	12	36.4%	22	22.0%
31-40 yrs	25	37.3%	6	18.2%	31	31.0%
> 40 yrs	27	40.3%	9	27.3%	36	36.0%
Total	67	100.0%	33	100.0%	100	100.0%

P-Value = 0.014 (Sig)

Sputum AFB	Diagnosis					
	Pulmonary TB		Extra PTB		Total	
	N	%	N	%	N	%
Negative	44	65.7%	19	57.6%	63	63.0%
1+	9	13.4%	0	0.0%	9	9.0%
2+	12	17.9%	0	0.0%	12	12.0%
3+	2	3.0%	0	0.0%	2	2.0%
NA	0	0.0%	14	42.4%	14	14.0%
Total	67	100.0 %	33	100.0 %	100	100.0%

P-Value = 0.001 (Highly Sig)

Sputum AFB	Diagnosis					
	Pulmonary TB		Extra PTB		Total	
	N	%	N	%	N	%
Negative	44	65.7%	19	57.6%	63	63.0%
Positive	23	34.3%	0	0.0%	23	23.0%
NA	0	0.0%	14	42.4%	14	14.0%
Total	67	100.0 %	33	100.0 %	100	100.0%

P-Value = 0.001 (Highly Sig)

ANA Report	Diagnosis					
	Pulmonary TB		Extra PTB		Total	
	N	%	N	%	N	%
Negative	57	85.1%	28	84.8%	85	85.0%
Positive	10	14.9%	5	15.2%	15	15.0%
Total	67	100.0 %	33	100.0 %	100	100.0%

P-Value = 0.976 (NS)

ANA Report	Diagnosis					
	Pulmonary TB		Extra PTB		Total	
	N	%	N	%	N	%
Negative	57	85.1%	28	84.8%	85	85.0%
Speckled 2+ pattern	7	10.4%	3	9.1%	10	10.0%
Speckled 3+ pattern	2	3.0%	1	3.0%	3	3.0%
Nucleolar 2+ pattern	1	1.5%	0	0.0%	1	1.0%
Pseudo centromere 2+ pattern	0	0.0%	1	3.0%	1	1.0%
Total	67	100.0 %	33	100.0 %	100	100.0%

P-Value = 0.633 (NS)

ANA REPORT * SPUTUM AFB

Crosstab								
			SPUTUM AFB					Total
			1+	2+	3+	NA	NEG	
ANA REPORT	NEG	Count	8	9	0	13	56	86
		% within ANA REPORT	9.3%	10.5%	.0%	15.1%	65.1%	100.0%
	NUCLEOLAR 2+	Count	0	1	0	0	0	1
		% within ANA REPORT	.0%	100.0%	.0%	.0%	.0%	100.0%
	PSEUDOCENTROMERE 2+	Count	0	0	0	0	1	1
		% within ANA REPORT	.0%	.0%	.0%	.0%	100.0%	100.0%
	SPECKLED 2+	Count	0	2	2	1	4	9
		% within ANA REPORT	.0%	22.2%	22.2%	11.1%	44.4%	100.0%
	SPECKLED 3+	Count	1	0	0	0	2	3
		% within ANA REPORT	33.3%	.0%	.0%	.0%	66.7%	100.0%
Total		Count	9	12	2	14	63	100
		% within ANA REPORT	9.0%	12.0%	2.0%	14.0%	63.0%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	33.317[a]	16	.007
Likelihood Ratio	20.613	16	.194
N of Valid Cases	100		

a. 20 cells (80.0%) have expected count less than 5. The minimum expected count is .02.

ANA REPORT * SEX

Crosstab

			SEX		Total
			F	M	
ANA REPORT	NEG	Count	25	61	86
		% within ANA REPORT	29.1%	70.9%	100.0%
	NUCLEOLAR 2+	Count	0	1	1
		% within ANA REPORT	.0%	100.0%	100.0%
	PSEUDOCENTROMERE 2+	Count	0	1	1
		% within ANA REPORT	.0%	100.0%	100.0%
	SPECKLED 2+	Count	5	4	9
		% within ANA REPORT	55.6%	44.4%	100.0%
	SPECKLED 3+	Count	1	2	3
		% within ANA REPORT	33.3%	66.7%	100.0%
Total		Count	31	69	100
		% within ANA REPORT	31.0%	69.0%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	3.593[a]	4	.464
Likelihood Ratio	3.958	4	.412
N of Valid Cases	100		

a. 7 cells (70.0%) have expected count less than 5. The minimum expected count is .31.

ANA STATUS * AFB CLASS

Crosstab

			AFB CLASS		
			NEGATIVE	POSITIVE	Total
ANA STATUS	NEGATIVE	Count	56	17	73
		% within ANA STATUS	76.7%	23.3%	100.0%
	POSITIVE	Count	7	6	13
		% within ANA STATUS	53.8%	46.2%	100.0%
Total		Count	63	23	86
		% within ANA STATUS	73.3%	26.7%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	2.945[a]	1	.086		
Continuity Correction[b]	1.893	1	.169		
Likelihood Ratio	2.697	1	.101		
Fisher's Exact Test				.100	.088
Linear-by-Linear Association	2.911	1	.088		
N of Valid Cases[b]	86				

a. 1 cells (25.0%) have expected count less than 5. The minimum expected count is 3.48.

b. Computed only for a 2x2 table

ANA REPORT * AFB CLASS

Crosstab

			AFB CLASS		
			NEGATIVE	POSITIVE	Total
ANA REPORT	NEG	Count	56	17	73
		% within ANA REPORT	76.7%	23.3%	100.0%
	NUCLEOLAR 2+	Count	0	1	1
		% within ANA REPORT	.0%	100.0%	100.0%
	PSEUDOCENTROMERE 2+	Count	1	0	1
		% within ANA REPORT	100.0%	.0%	100.0%
	SPECKLED 2+	Count	4	4	8
		% within ANA REPORT	50.0%	50.0%	100.0%
	SPECKLED 3+	Count	2	1	3
		% within ANA REPORT	66.7%	33.3%	100.0%
Total		Count	63	23	86
		% within ANA REPORT	73.3%	26.7%	100.0%

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Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	5.824[a]	4	.213
Likelihood Ratio	5.732	4	.220
N of Valid Cases	86		

a. 7 cells (70.0%) have expected count less than 5. The minimum expected count is .27.

ANA STATUS * SPUTUM AFB

Crosstab

			SPUTUMAFB				
			1+	2+	3+	NEG	Total
ANA STATUS	NEGATIVE	Count	8	9	0	56	73
		% within ANA STATUS	11.0%	12.3%	.0%	76.7%	100.0%
	POSITIVE	Count	1	3	2	7	13
		% within ANA STATUS	7.7%	23.1%	15.4%	53.8%	100.0%
Total		Count	9	12	2	63	86
		% within ANA STATUS	10.5%	14.0%	2.3%	73.3%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	13.044[a]	3	.005
Likelihood Ratio	9.324	3	.025
N of Valid Cases	86		

a. 4 cells (50.0%) have expected count less than 5. The minimum expected count is .30.

ANA REPORT * SPUTUM AFB

Crosstab

			SPUTUMAFB				Total
			1+	2+	3+	NEG	
ANA REPORT	NEG	Count	8	9	0	56	73
		% within ANA REPORT	11.0%	12.3%	.0%	76.7%	100.0%
	NUCLEOLAR 2+	Count	0	1	0	0	1
		% within ANA REPORT	.0%	100.0%	.0%	.0%	100.0%
	PSEUDOCENTROMERE 2+	Count	0	0	0	1	1
		% within ANA REPORT	.0%	.0%	.0%	100.0%	100.0%
	SPECKLED 2+	Count	0	2	2	4	8
		% within ANA REPORT	.0%	25.0%	25.0%	50.0%	100.0%
	SPECKLED 3+	Count	1	0	0	2	3
		% within ANA REPORT	33.3%	.0%	.0%	66.7%	100.0%
Total		Count	9	12	2	63	86
		% within ANA REPORT	10.5%	14.0%	2.3%	73.3%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	30.322[a]	12	.002
Likelihood Ratio	18.951	12	.090
N of Valid Cases	86		

a. 16 cells (80.0%) have expected count less than 5. The minimum expected count is .02.

Oneway

Descriptives

AGE (YEARS)

	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
NEGATIVE	86	36.93	11.000	1.186	34.57	39.29	3	50
SPECKLED 2+	9	29.44	10.382	3.461	21.46	37.42	20	50
SPECKLED 3+	3	43.00	5.196	3.000	30.09	55.91	40	49
NUCLEOLAR 2+	1	23.00	.	.	.	.	23	23
PSEUDOCENTROMERE 2+	1	43.00	.	.	.	.	43	43
Total	100	36.36	11.017	1.102	34.17	38.55	3	50

ANOVA

AGE (YEARS)					
	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	813.236	4	203.309	1.724	.151
Within Groups	11201.804	95	117.914		
Total	12015.040	99			

Group Statistics

	ANA STATUS	N	Mean	Std. Deviation	Std. Error Mean
AGE (YEARS)	NEGATIVE	86	36.93	11.000	1.186
	POSITIVE	14	32.86	10.848	2.899

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
AGE (YEARS)	Equal variances assumed	.035	.852	1.287	98	.201	4.073	3.164	-2.207	10.353
	Equal variances not assumed			1.300	17.641	.210	4.073	3.132	-2.517	10.664

ANA STATUS * SEX Cross tabulation

			SEX		Total
			F	M	
ANA STATUS	NEGATIVE	Count	25	61	86
		% within ANA STATUS	29.1%	70.9%	100.0%
	POSITIVE	Count	6	8	14
		% within ANA STATUS	42.9%	57.1%	100.0%
Total		Count	31	69	100
		% within ANA STATUS	31.0%	69.0%	100.0%

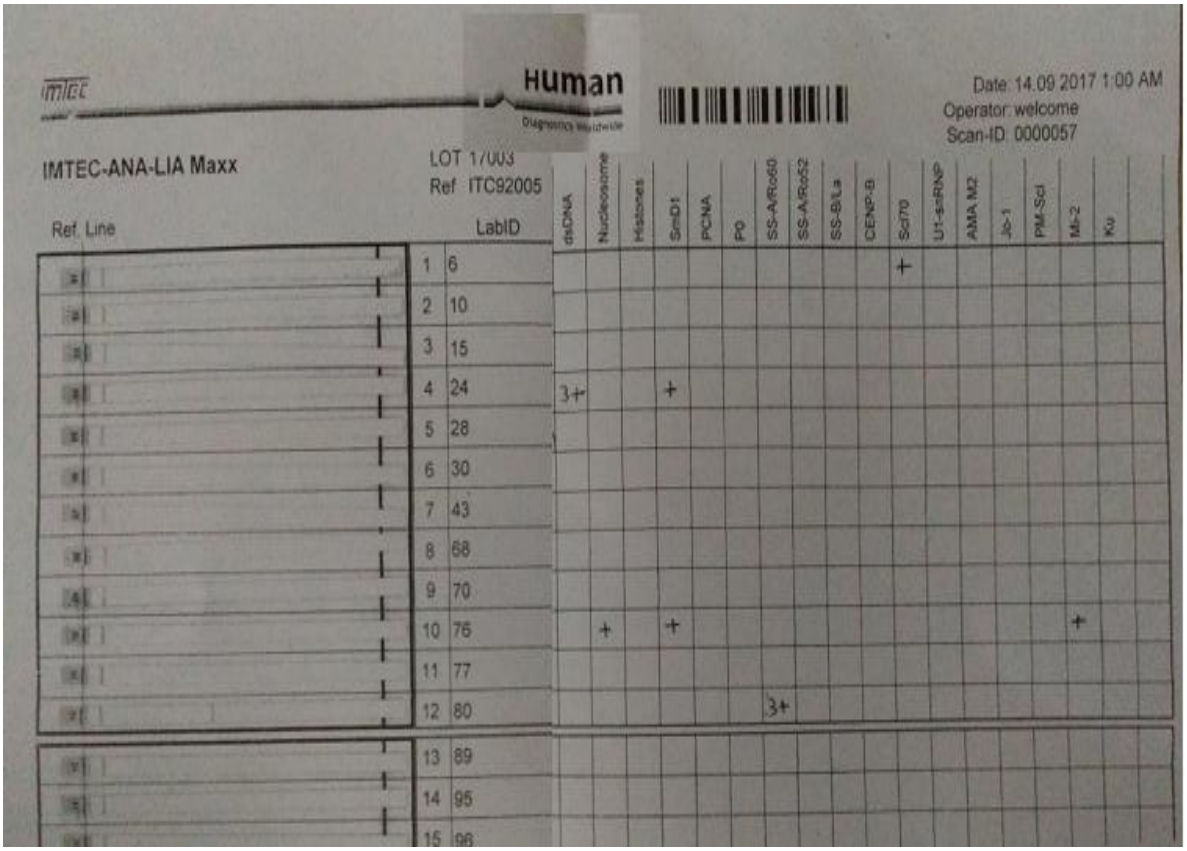
Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	1.070[a]	1	.301		
Continuity Correction[b]	.522	1	.470		
Likelihood Ratio	1.021	1	.312		
Fisher's Exact Test				.354	.231
N of Valid Cases[b]	100				

a. 1 cells (25.0%) have expected count less than 5. The minimum expected count is 4.34.

b. Computed only for a 2x2 table

ANA PROFILING:



Significant Autoantibodies identified in ANA Profiling

- One patient (A 20 years old male with sputum AFB 2+ PTB) had ds DNA 3+
- One patient (A 40 year old female with sputum AFB 3+ PTB relapse) had SS – A / Ro 3+

Insignificant Autoantibodies identified in ANA Profiling

- Scl 70 1+
- Nucleosomes 1+
- SmD 1 1+; Mi – 2 1+

DISCUSSION

DISCUSSION

There is a complex relationship between Mycobacterium tuberculosis and autoimmune diseases. Initial studies had shown that patients with SLE had higher risk of development of tuberculosis. Gaitonde et al and Agarwal et al had reported that the risk of TB in SLE was 10 to 60 fold higher than the general population.[1,2] The clinical symptoms of fever, malaise and weight loss are common to both TB and SLE. Tuberculosis is often more severe in patients with SLE. Extrapulmonary and disseminated TB is more common in SLE. Treatment of SLE with corticosteroids and TNF alpha inhibitors increases the risk of TB[3,4] . Since there is an overlap of symptoms of tuberculosis and SLE, there is a delay in diagnosis. Identification of latent tuberculosis infection is essential so that patients can be started on INH prophylaxis. Identification of latent tuberculosis infection is best done by using IGRA test. The advantages of using IGRA test are due to the use of Mycobacterium tuberculosis specific antigen thereby allowing distinction of infection of Mycobacterium tuberculosis from immunity towards BCG vaccine or Non tuberculous mycobacteria[5,6]. SLE is both precipitated and exacerbated by tuberculosis. Anti-TB drugs like INH, Rifampicin and PAS induce lupus like syndrome called Drug induced lupus. The presenting features of drug induced lupus includes lymphadenopathy, fever, erythematous malar rash and pleural

effusion, starting with at least one month continuous exposure of anti-TB drugs till even one year after starting anti-TB drugs[7]. Investigations may show anemia, leucopenia, altered LFT, positive ANA and Anti histone antibody. Clinical lupus occurs in less than 1% patients who need discontinuation of treatment with the offending drug. Of the patients treated with INH about 20% develop autoantibodies[8]. Several studies have shown that Mycobacterial infections induce the development of autoantibodies[10].

The mechanisms of development of autoantibodies are under study. The neutrophil lysosomal enzymes are released by the generation of oxygen metabolites due to interaction between neutrophils and phenol glycolipids of the cell wall of Mycobacterium tuberculosis, thereby releasing the agranular components of the neutrophils which causes development of antibodies against them[11].Heat Shock Protein as a trigger for autoantibodies has also been postulated[20].The autoantibodies that have been reported includes both disease specific and disease nonspecific like RF, ANA, ANCA, Anti cardiolipin antibody and Anticyclic citrullinated peptide[12,13,14,15,16,17]. Studies have reported 34% ANCA and 24.3% ANA positivity with tuberculous infection[18]. In TB pleural effusion also ANA positivity has been demonstrated[19]. Diseases like Infective endocarditis, infections and malignancy can also produce autoantibodies like RF and

antiphospholipid syndromes[21,22]. Prevalence of ANA positivity in general population in India was 12.3 % as per Minz R.W et al[41]. The clinical features and radiological findings of tuberculosis was not changed by the presence of autoantibodies[23]. The autoantibody levels returned to normal following treatment with anti-TB drugs and did not need immunosuppressive therapy[24]. Autoantibodies was not associated with clinical symptoms of autoimmune diseases. In contrast the titers of autoantibodies often increases with flare of disease activity like Anti – ds DNA in lupus nephritis[25]. Recently disseminated TB in a case of SLE with negative ANA and positive Anti- ds DNA has been reported[26].

In the present study, 100 tuberculosis patients were evaluated. Male patients were 69 % of the study population and female patients constituted 31 % of study population. Among males, Pulmonary TB was diagnosed in 47 patients and extrapulmonary TB was diagnosed in 22 patients. Among females, Pulmonary TB was diagnosed in 20 patients and extrapulmonary TB in 11 patients.Most of the patients were above 40 years age group: 11 % patients were aged about 20 years, 22 % patients were in the age group of 21-30 years, 31% patients were in the age group of 31-40 years, 36% patients were in the age group of more than 40 years. Majority of PTB occurred in above 40 years age group. In the pulmonary TB group, 5 patients were aged 20 years; 10 patients were in 21-30 years group; 25

patients were in 31-40 years group; 27 patients were in above 40 years age group. Majority of EPTB occurred in 21-30 years age group. In the extrapulmonary TB group, 6 patients were aged 20 years; 12 patients were in 21-30 years group; 6 patients were in 31-40 years group; 9 patients were above 40 years.

Among the 100 patients, Pulmonary TB was the common diagnosis with about 67% of the cases. 55 patients were newly diagnosed, 3 patients were defaulters and 9 patients were relapsed cases. The most commonly identified symptoms were fever; cough with expectoration; loss of weight and appetite. Sputum AFB was positive in 23 patients with predominant 2+ sputum positive cases. Among the 33 extrapulmonary cases, the most common diagnosis was TB pleural effusion with 10 patients; 8 patients with TB lymphadenitis; 8 patients with skeletal TB and 7 cases of other system involvement. Of the 100 patients, 15 patients were ANA positive; 10 patients with pulmonary TB and 5 patients with extrapulmonary TB. The most common pattern identified was speckled pattern (13 patients). Nucleolar pattern was seen in 1 patient and pseudo centromere pattern was seen in 1 patient. Pseudo centromere pattern is usually not seen in autoimmune diseases. None of the patients had symptoms or signs of connective tissue disorder. Significant association was found between ANA report and sputum AFB.ANA profiling done for the 15 ANA positive

cases showed significant specific autoantibodies in 2 cases. 1 patient (A 20 years old male with sputum AFB 2+ PTB) had Anti-ds DNA which is a specific antibody for SLE and 1 patient (A 40 year old female with sputum AFB 3+ PTB relapse) had SS-A/ Ro which is a specific antibody for Sjogren's syndrome. Other autoantibodies detected in insignificant values were Scl 70, nucleosomes, Anti-SmD and Mi-2.

LIMITATIONS OF STUDY

1. We found that in our study there were some limitations with the sample size which precluded us from getting statistical significance with regard to certain variables.
2. In our study follow up of patients after initiating anti-TB drugs and analysis of its effect on ANA positivity has to be done.
3. Male patients were represented higher than female patients.
4. Follow up of patients to assess for the development of symptoms and signs of connective tissue disease has to be done.

CONCLUSION

- The incidence of ANA positivity from this study was 15 %.
- Tuberculosis and autoimmune diseases have a complex relationship with one another.
- There is higher risk of tuberculosis in patients with autoimmune diseases which may be related to the disease process; immunosuppression by the drugs used for treatment of autoimmune diseases.
- In turn tuberculosis can precipitate autoimmune diseases.
- The symptoms of tuberculosis overlaps with the symptoms of connective tissue disorders causing a delay in diagnosis.
- Autoantibodies can develop in tuberculosis even in the absence of the symptoms and specific autoantibodies of connective tissue disorders.

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ANNEXURES

- PROFORMA
- ETHICAL COMMITTEE APPROVAL FORM
- PLAGIARISM SCREENSHOT
- PLAGIARISM CERTIFICATE
- INFORMATION SHEET
- CONSENT FORM
- MASTER CHART

PROFORMA: INCIDENCE OF AUTOIMMUNITY IN TUBERCULOSIS

Patient ID No. :

Name :

Age/Sex :

OP/IP No :

Weight :

Diagnosis :

Duration :

SYMPTOMS:

- Cough with sputum for > 2 weeks
- Fever for > 2 weeks
- Hemoptysis
- Weight loss
- Arthralgia
- Early morning stiffness
- Joint swelling
- Skin rashes
- Mucosal ulcers
- Dry eyes and mouth
- Hair loss

SIGNS:

- Joint swelling and restriction of movements
- Nail changes
- Skin changes
- Alopecia
- Muscle weakness

INVESTIGATIONS:

BLOOD COUNTS -	Total count DC ESR Hemoglobin
Random Blood Sugar	
Renal Function Test –	Urea Creatinine
Liver function test -	Total bilirubin Direct bilirubin SGOT SGPT ALP Total Protein Albumin
Electrolytes	Sodium Potassium Calcium

Chest X ray	
USG KUB	
Sputum AFB	
Sputum gene Xpert	
Tissue / fluid AFB	
Tissue / fluid Gene Xpert	
HPE	
Others	
ANA report	

ETHICAL COMMITTEE APPROVAL FORM

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI 600 003

EC Reg.No.ECR/270/Inst./TN/2013
Telephone No.044 25305301
Fax: 011 25363970

CERTIFICATE OF APPROVAL

To
Dr.K.B. Shreeja
I Year PG in MD General Medicine
Institute of Internal Medicine
Madras Medical College
Chennai 600 003

Dear Dr.K.B.Shreeja,

The Institutional Ethics Committee has considered your request and approved your study titled **"INCIDENCE OF AUTOIMMUNITY IN TUBERCULOSIS "**
NO.31032017(I)

The following members of Ethics Committee were present in the meeting hold on **02.03.2017** conducted at Madras Medical College, Chennai 3

1.Dr.C.Rajendran, MD.,	:Chairperson
2.Dr. K.Narayanasamy,MD,DM.,Dean(FAC), MMC,Ch-3	:Deputy Chairperson
3.Prof.Sudha Seshayyan,MD., Vice Principal,MMC,Ch-3	: Member Secretary
4.Prof.S.Suresh, MS, Prof. of Surgery,MMC,Ch-3	: Member
5.Prof.Baby Vasumathi,MD.,Director, Inst. of O & G	: Member
6.Prof.K.Ramadevi,MD.,Director,Inst.of Bio-Che,MMC,Ch-3	: Member
7.Prof.R.Padmavathy, MD, Director,Inst.of Pathology,MMC,Ch-3	: Member
8.Tmt.J.Rajalakshmi, JAO,MMC, Ch-3	: Lay Person
9.Thiru S.Govindasamy, BA.,BL,High Court,Chennai	: Lawyer
10.Tmt.Arnold Saulina, MA.,MSW.,	:Social Scientist

We approve the proposal to be conducted in its presented form.

The Institutional Ethics Committee expects to be informed about the progress of the study and SAE occurring in the course of the study, any changes in the protocol and patients information/informed consent and asks to be provided a copy of the final report.

Member Secretary – Ethics Committee

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE
CHENNAI-600 003.

PLAGIARISM SCREENSHOT

Urkund Analysis Result

Analysed Document: urkund upload - Copy.docx (D31303176)
Submitted: 10/13/2017 6:52:00 PM
Submitted By: shreejakb@yahoo.com
Significance: 1 %

Sources included in the report:

THESIS COMBINED.docx (D22977108)
final.docx (D29353916)

Instances where selected sources appear:

3

PLAGIARISM CERTIFICATE

This is to certify that this dissertation work titled **"INCIDENCE OF AUTOIMMUNITY IN TUBERCULOSIS"** of the candidate **DR.K.B.SHREEJA** with registration Number **201511013** for the award of **M.D** in the branch of **GENERAL MEDICINE.I** personally verified the urkund.com website for the purpose of plagiarism Check. I found that the uploaded thesis file contains from introduction to conclusion pages and result shows 1 percentage of plagiarism in the dissertation.

Guide & Supervisor sign with Seal.

INFORMATION SHEET

We are conducting a study on **"INCIDENCE OF AUTOIMMUNITY IN TUBERCULOSIS"** among patients attending Rajiv Gandhi Government General Hospital, Chennai and for that your specimen may be valuable to us.

The purpose of this study is to identify the association between Tuberculosis and Autoimmune disorders.

We are selecting certain cases and if you are found eligible, we may perform extra tests and special studies which in any way do not affect your final report or management.

The privacy of the patients in the research will be maintained throughout the study. In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared.

Taking part in this study is voluntary. You are free to decide whether to participate in this study or to withdraw at any time; your decision will not result in any loss of benefits to which you are otherwise entitled.

The results of the special study may be intimated to you at the end of the study period or during the study if anything is found abnormal which may aid in the management or treatment.

Signature of Investigator Signature of Participant

Date:

Place:

PATIENT CONSENT FORM

Study Detail	:	**INCIDENCE OF AUTOIMMUNITY IN TUBERCULOSIS**
Study Centre	:	Rajiv Gandhi Government General Hospital, Chennai.

Patient's Name :
Patient's Age :
Identification Number

Patient may check (☑) these boxes

- I confirm that I have understood the purpose of procedure for the above study. I have the opportunity to ask question and all my questions and doubts have been answered to my complete satisfaction. ☐
- I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving reason, without my legal rights being affected. ☐
- I understand that sponsor of the clinical study, others working on the sponsor's behalf, the ethical committee and the regulatory authorities will not need my permission to look at my health records, both in respect of current study and any further research that may be conducted in relation to it, even if I withdraw from the study I agree to this access. However, I understand that my identity will not be revealed in any ☐

information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from this study.

- I agree to take part in the above study and to comply with the instructions given during the study and faithfully cooperate with the study team and to immediately inform the study staff if I suffer from any deterioration in my health or wellbeing or any unexpected or unusual symptoms. ☐
- I hereby consent to participate in this study. ☐
- I hereby give permission to undergo complete clinical examination and diagnostic tests including hematological, biochemical, radiological tests. ☐

Signature/thumb impression:

Patient's Name and Address:

Signature of Investigator:

(Dr. K. B. Shreeja)

MASTER CHART

MASTER CHART:

7	6	5	4	3	2	1	**S.No**
F	F	M	M	M	M	M	**SEX**
25	24	21	35	40	35	33	**AGE (YEARS)**
TB OSTEOMY ELITIS	ABDOMINAL TB	LUPUS VULGARIS	PTB	PTB	SPINAL TB	PTB	**DIAGNOSIS**
2	2	3	1	4	4	3	**DURATION (MONTHS)**
NEG	NEG	NEG	SPECKLED 2+	NEG	NEG	NEG	**ANA REPORT**
NEG	NA	NA	NEG	2+	NA	NEG	**SPUTUM AFB**
			Scl 70 (1+)				**ANA PROFILING**

16	15	14	13	12	11	10	9	8
F	M	F	M	M	M	M	M	F
20	25	34	40	26	30	42	40	23
PTB	PTB	PTB	PTB	OCULAR TB	DISSEMI-NATED TB	SPINAL TB	TB PLEURAL EFFUSION	TB LYMPH - ADENITIS
2	1	1	1	2	6	5	2	6
NEG	NEG	NEG	SPECKLED 3+	NEG	NEG	NEG	NEG	SPECKLED 2+
NEG	NEG	NEG	NEG	NA	NEG	NA	NEG	NA
			NEGATIVE					NEGATIVE

26	25	24	23	22	21	20	19	18	17
F	F	F	F	M	F	M	M	M	M
22	26	42	38	20	40	30	39	40	43
PTB / LARYNGEAL TB	TB PLEURAL EFFUSION	PTB	PTB	PTB	PTB	PTB	PTB	PTB	PTB
6	1	2.5	3	4	1	1.5	4	3	2
NEG	NEG	NEG	NEG	SPECKLED 2+	NEG	NEG	NEG	NEG	NEG
NEG	NEG	NEG	NEG	2+	NEG	NEG	NEG	NEG	NEG
				DS-DNA (3+); SmD1(1+)					

35	34	33	32	31	30	29	28	27
M	M	F	M	M	F	M	M	F
49	26	36	31	25	20	50	23	42
PTB RELAPSE	TB LYMPHAD-ENITIS	TB PLEURAL EFFUSION	PTB	PTB	PTB	PTB	PTB	PTB
5	2	2	1	3	2	2	1	2
NEG	NEG	NEG	NEG	NEG	SPECKLED 2+	NEG	NUCLEOLAR 2+	NEG
NEG	NA	NEG	NEG	NEG	NEG	1+	2+	NEG
					NEGATIVE		NEGATIVE	

46	45	44	43	42	41	40	39	38	37	36
M	M	F	M	M	M	M	M	M	F	M
50	33	20	49	50	49	50	50	38	27	37
PTB RELAP-SE	PTB DEFA-ULTER	TB LYMP-HADE	TB PLEURAL EFFUSION	TB PLEURAL EFFUSION	PTB	PTB	PTB	PTB	PTB	PTB RELAP-SE
2	8	6	1	1	2	1	2	1	1	4
NEG	NEG	NEG	SPECKLED 3+	NEG	NEG	NEG	NEG	NEG	NEG	NEG
NEG	2+	NEG	NEG	NEG	2+	1+	1+	NEG	NEG	2+
			NEGATIVE							

57	56	55	54	53	52	51	50	49	48	47
M	M	F	F	M	M	M	M	M	M	F
24	31	27	34	50	50	40	50	50	20	50
TB PLEURAL EFFUSION	PTB	PTB	PTB	PTB RELAPSE	PTB	TB LYMP-HADE	PTB	PTB	TB SPINE	PTB
2	1	2.5	2	1 WEEK	1	1	1	4	4	4
NEG	NEG	NEG	NEG	NEG	NEG	NEG	NEG	NEG	NEG	NEG
NEG	NEG	NEG	NEG	2+	NEG	NA	NEG	NEG	NEG	NEG

66	65	64	63	62	61	60	59	58
F	M	M	F	M	M	M	M	M
27	50	50	20	40	50	22	20	40
PTB	TB PLEURAL EFFUSION	PTB/ OLD CVA	PTB	PTB	PTB RELAPSE	TB LYMPH-ADENITIS	TB SACROILITIS	PTB
1	2	2	3	2	2 WEEKS	4	1.5	1.5
SPECKLED 2+	NEG	NEG	NEG	NEG	NEG	NEG	NEG	NEG
3+	NEG	NEG	1+	NEG	2+	NA	NEG	NEG
NEGATIVE								

75	74	73	72	71	70	69	68	67
F	M	M	F	M	F	M	M	M
50	40	38	50	45	35	50	29	50
PTB	TB SPONDYLO-DISCITIS	PTB	TB LYMPH-ADENITI	PTB	PTB RELAPSE	PTB RELAPSE	COLD ABSCESS CHEST	PTB
2	6	2	4	1	3	1	4	1
SPECKLED 2+	SPECKLED 2+	NEG	NEG	NEG	NEG	NEG	SPECKLED 2+	NEG
2+	NEG	NEG	NA	1+	2+	2+	NEG	NEG
NEGATIVE	NUCLEOSO-MES (1+), SmD1 (1+), Mi-2 (1+)						NEGATIVE	

84	83	82	81	80	79	78	77	76
F	F	M	M	M	M	F	M	F
20	50	47	41	40	34	40	50	20
TB LYMPH-ADENITIS	PTB	PTB	PTB	PTB DEFAULTER	PTB	PTB RELAPSE	TB PLEURAL EFFUSION	OCUL-AR TB
1.5	1	3	3	1.5	1.5	4	3	3 WEEKS
NEG	NEG	NEG	NEG	NEG	NEG	SPECKLED 3+	NEG	NEG
NEG	NEG	1+	2+	NEG	1+	1+	NEG	NA
						SSA/Ro (3+)		

92	91	90	89	88	87	86	85
F	F	M	M	M	F	F	M
40	40	50	48	35	21	20	24
PTB	SACRAL TB OSTEOMYELITIS	ILEO-CAECAL TB	TB OSTEO-MYELITIS	PTB	PTB DEFAULTER / 7 MONTHS ANTENATAL	TB LYMPH-ADENITIS	TB PLEURAL EFFUSION
1	2	2	4	3	6	1	20 DAYS
NEG	NEG	NEG	NEG	NEG	SPECKLED 2+	NEG	NEG
1+	NA	NEG	NA	NEG	3+	NA	NEG
					NEGATIVE		

100	99	98	97	96	95	94	93
M	M	M	M	M	M	M	M
43	40	41	30	50	3	46	43
PTB	PTB	PTB	PTB	PTB RELAPSE	PTB	PTB	TB PLEURAL EFFUSION
4	3	2	1	1	2.5	2	1
NEG	NEG	NEG	NEG	NEG	NEG	SPECK-LED (2+)	PSEUDO-CENTROMERE 2+
NEG	NEG	NEG	NEG	NEG	NEG	NEG	NEG
						NEGA-TIVE	NEGATIVE